METABOLIC SYNDROME and PREDIABETES

Robert Day MD FACP

METABOLIC SYNDROME
and
PREDIABETES

Goals of presentation

- define metabolic syndrome
- understand the clinical implications for increased risk of diabetes and cardiovascular disease
- recognize the public health implications of this condition
- develop a strategy to recognize metabolic syndrome and do something to manage it

The Insulin Resistance Syndrome

Clinical Manifestations

Central obesity
Glucose intolerance
Atherosclerosis
Hypertension
Polycystic ovary syndrome

Biochemical Abnormalities

Carbohydrate:

Insulin resistance
Hyperinsulinemia

Lipid:

High TG
Low HDL-C
Small, dense LDL particles

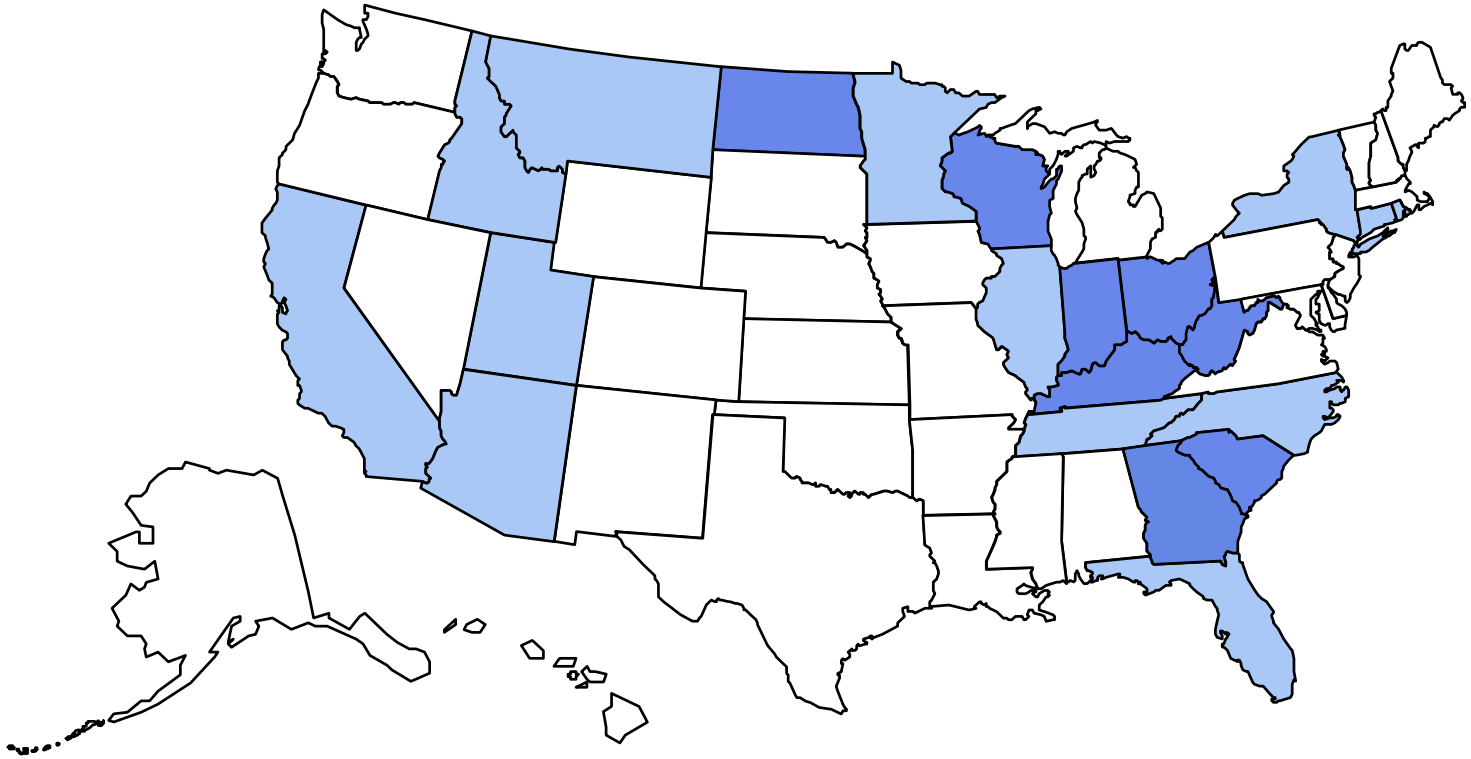
Fibrinolysis:

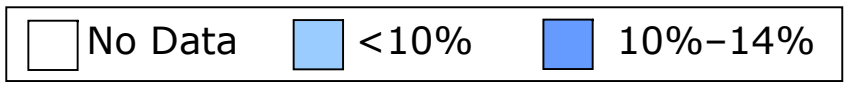
Increased PAI-1

Obesity Trends* Among U.S. Adults

BRFSS, 1985

(*BMI ≥30, or ~ 30 lbs overweight for 5’ 4” woman)



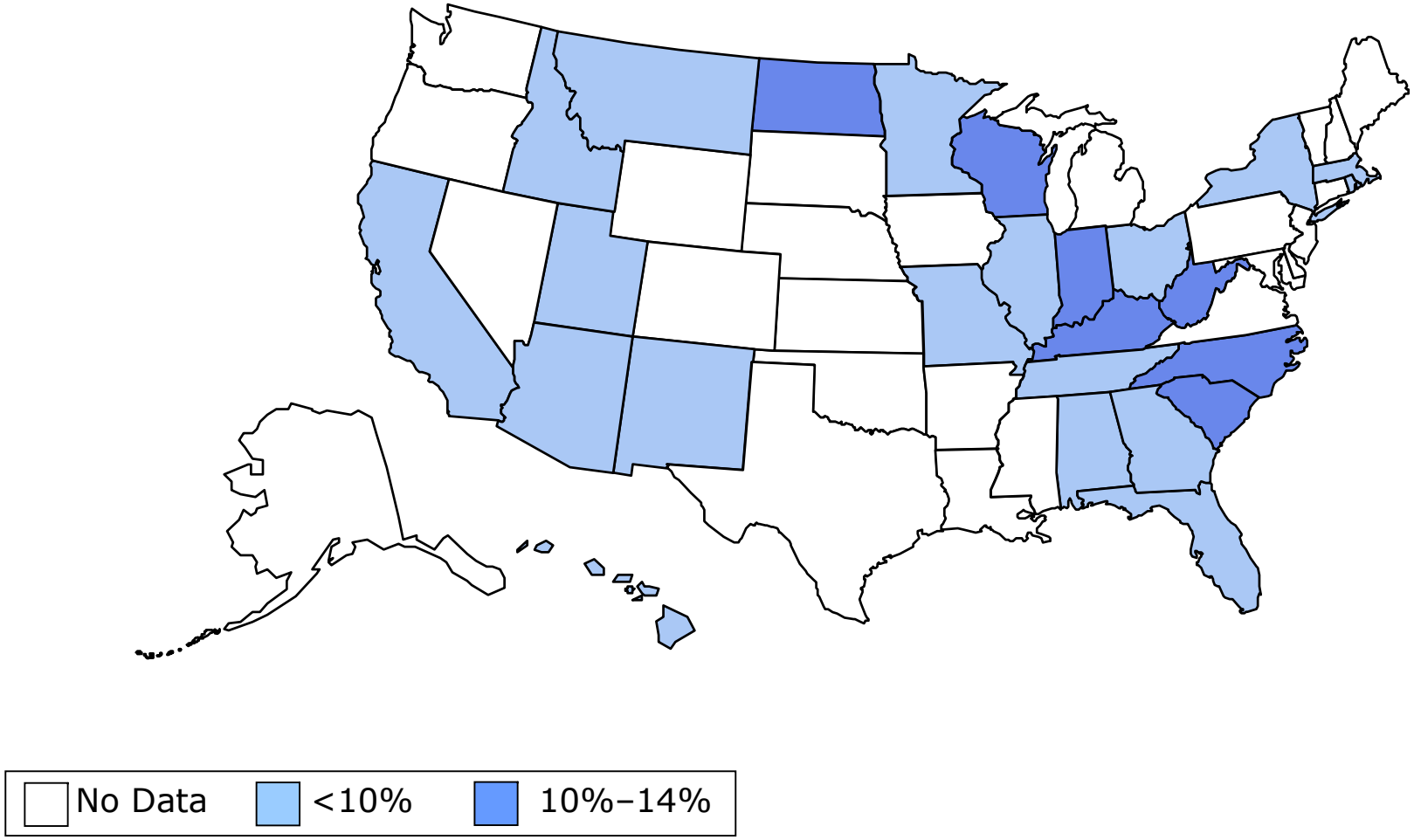


BRFSS: CDC program, Behavioral Risk Factor Surveillance Survey

Obesity Trends* Among U.S. Adults

BRFSS, 1986

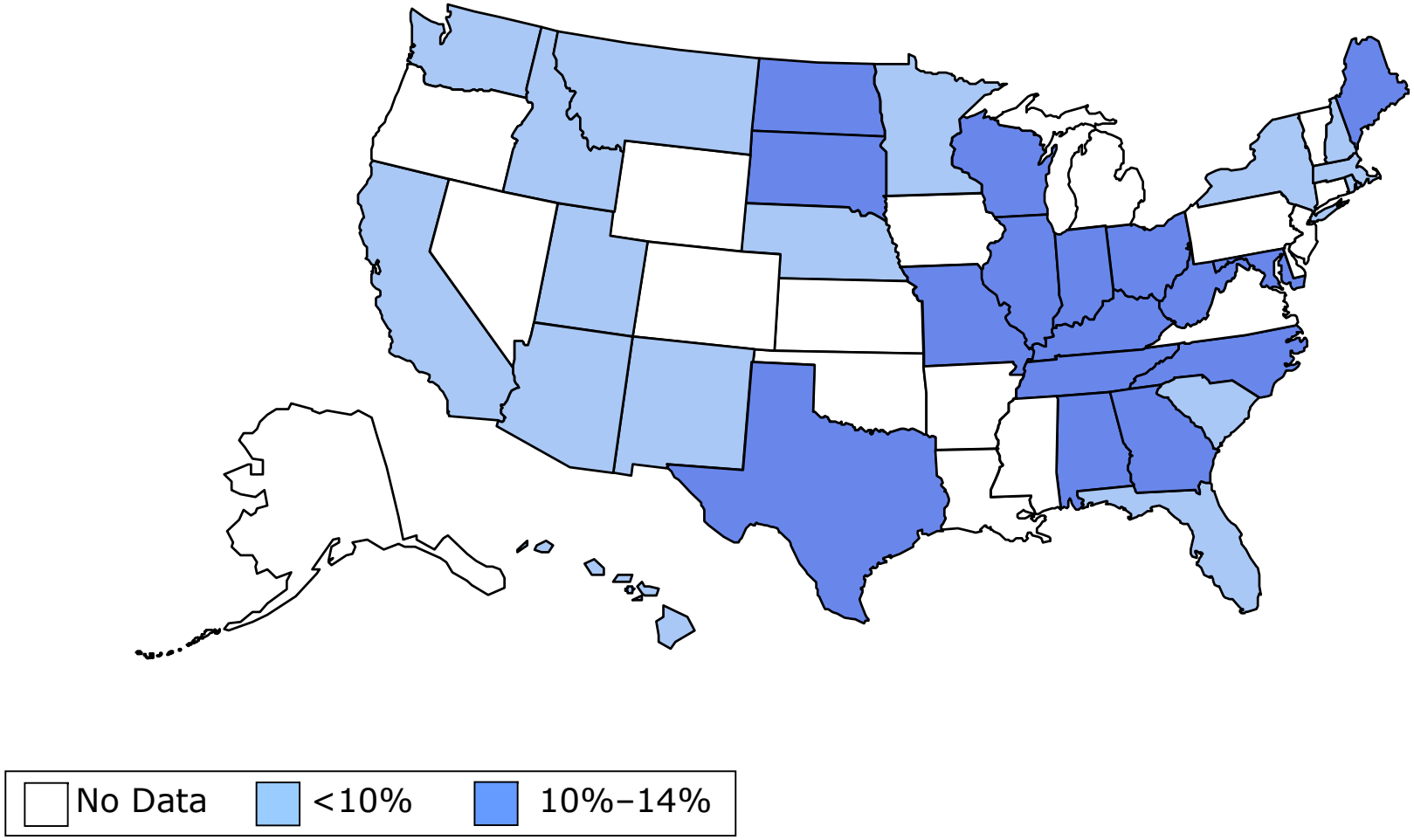
(*BMI ≥30, or ~ 30 lbs overweight for 5’ 4” woman)



Obesity Trends* Among U.S. Adults

BRFSS, 1987

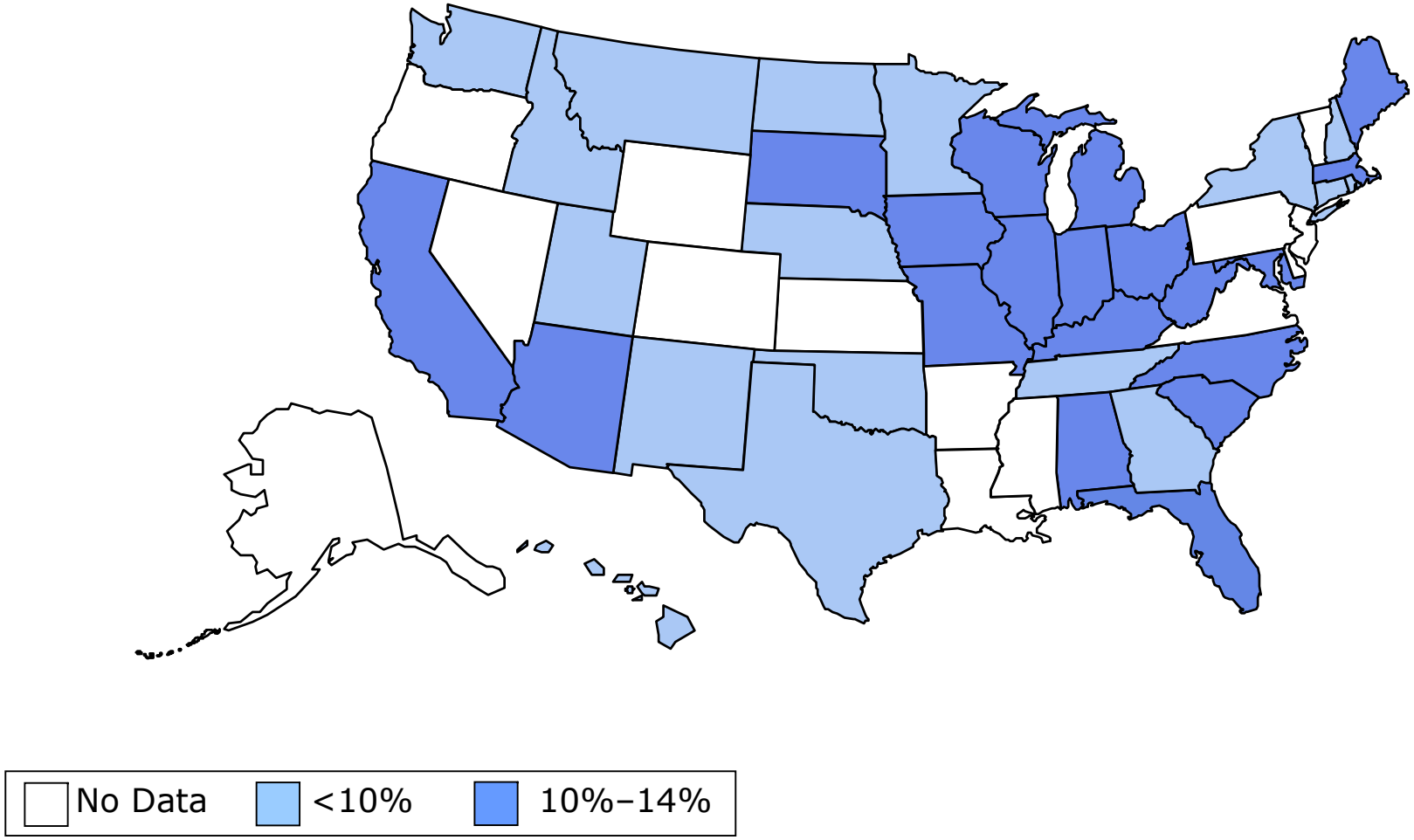
(*BMI ≥30, or ~ 30 lbs overweight for 5’ 4” woman)



Obesity Trends* Among U.S. Adults

BRFSS, 1988

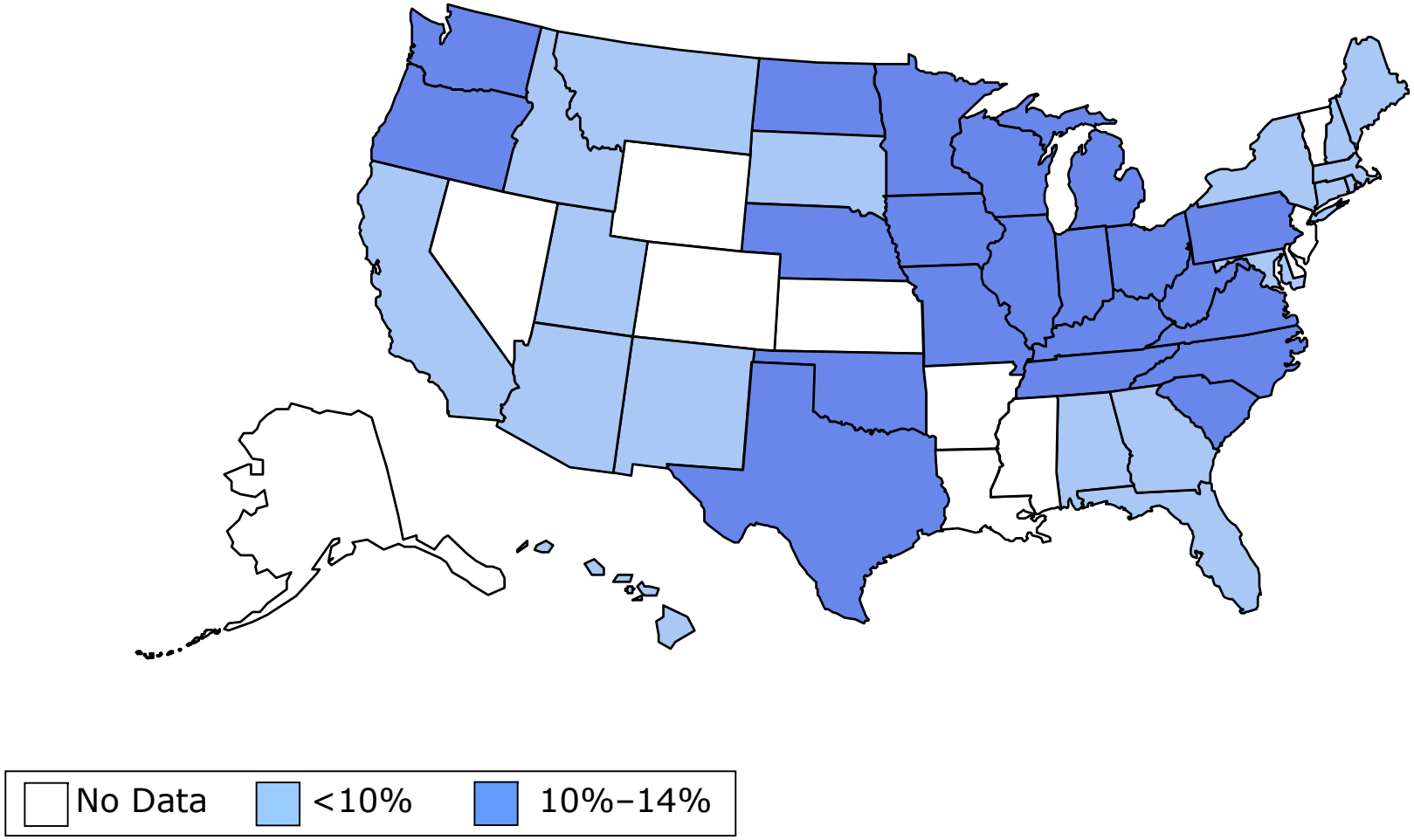
(*BMI ≥30, or ~ 30 lbs overweight for 5’ 4” woman)



Obesity Trends* Among U.S. Adults

BRFSS, 1989

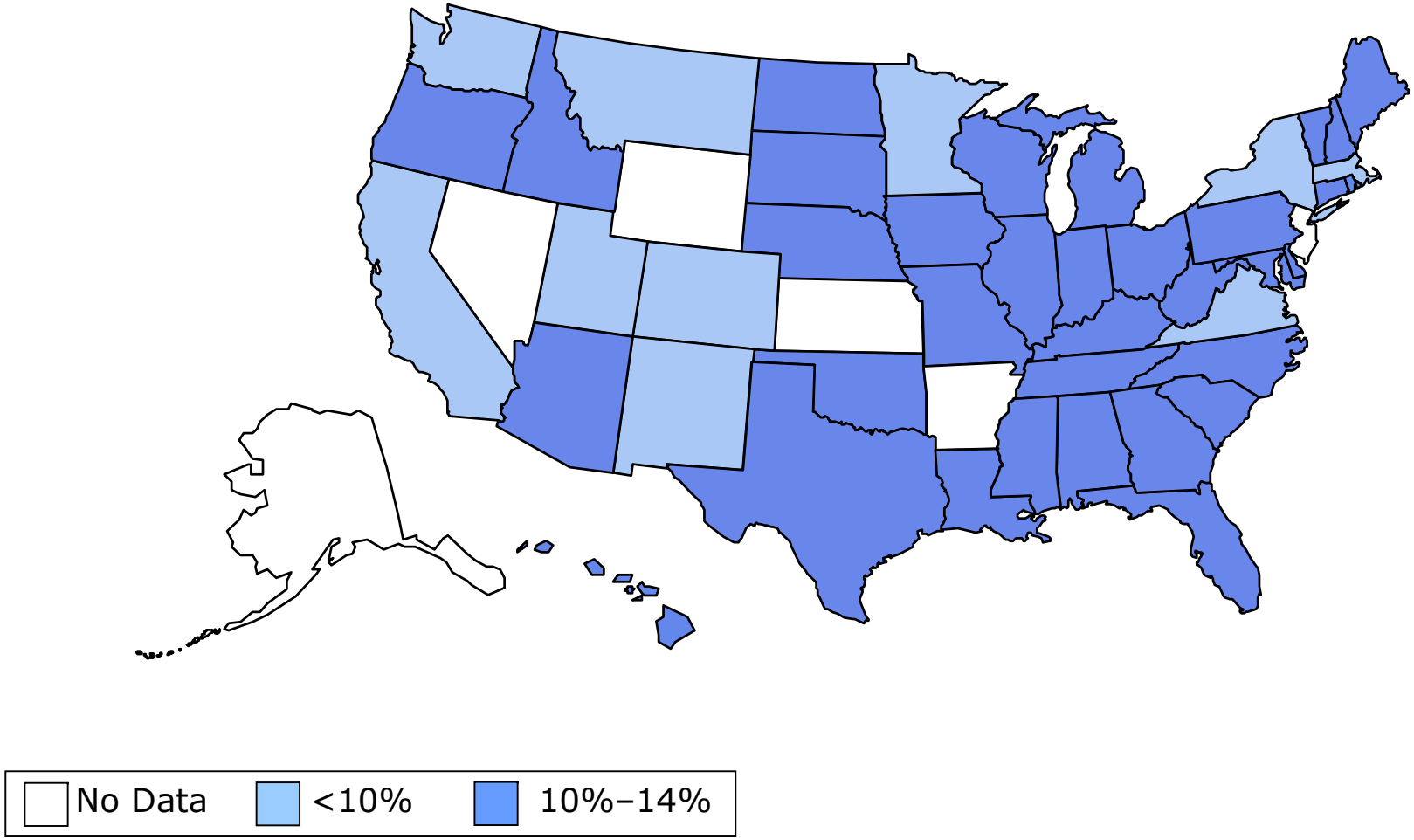
(*BMI ≥30, or ~ 30 lbs overweight for 5’ 4” woman)



Obesity Trends* Among U.S. Adults

BRFSS, 1990

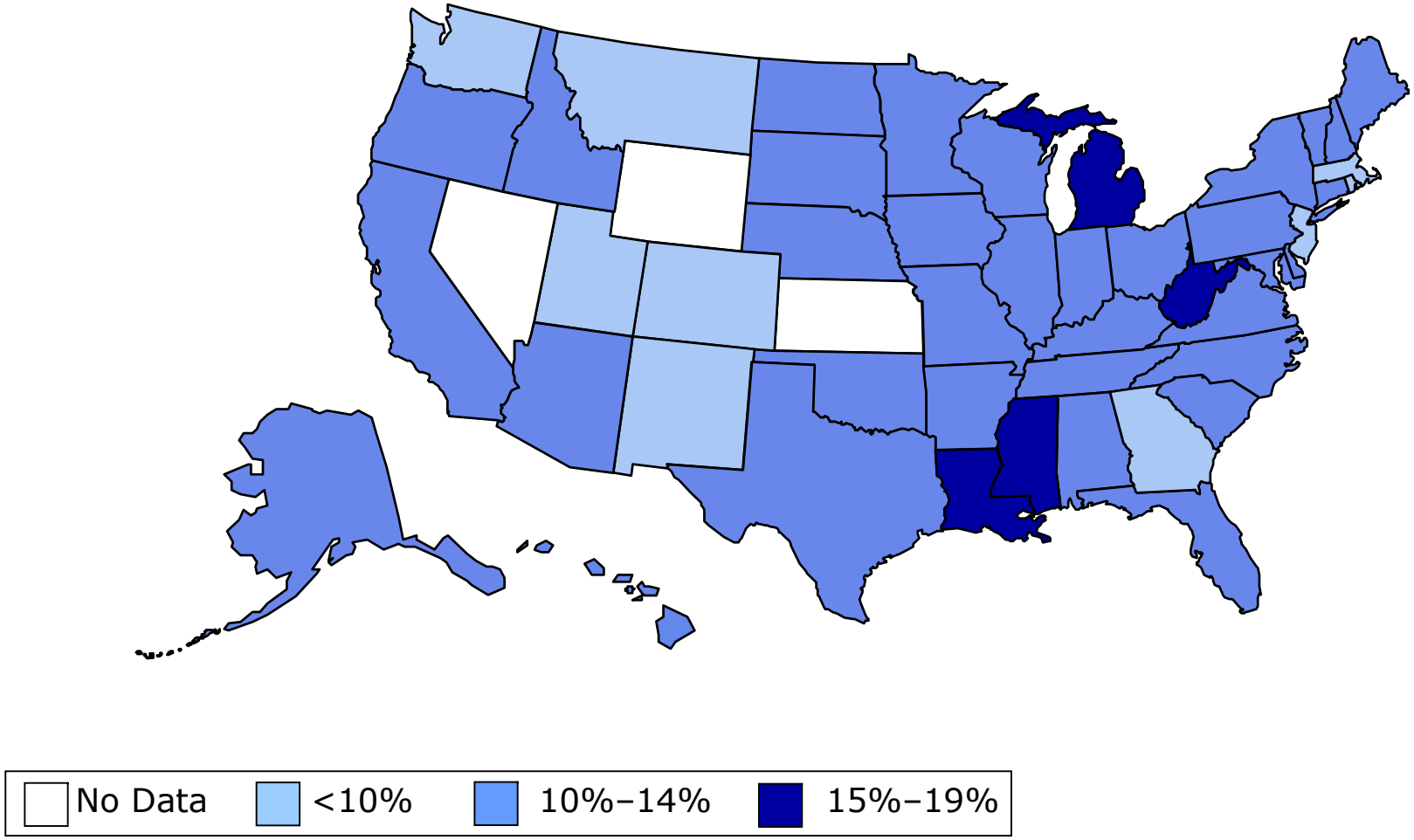
(*BMI ≥30, or ~ 30 lbs overweight for 5’ 4” woman)



Obesity Trends* Among U.S. Adults

BRFSS, 1991

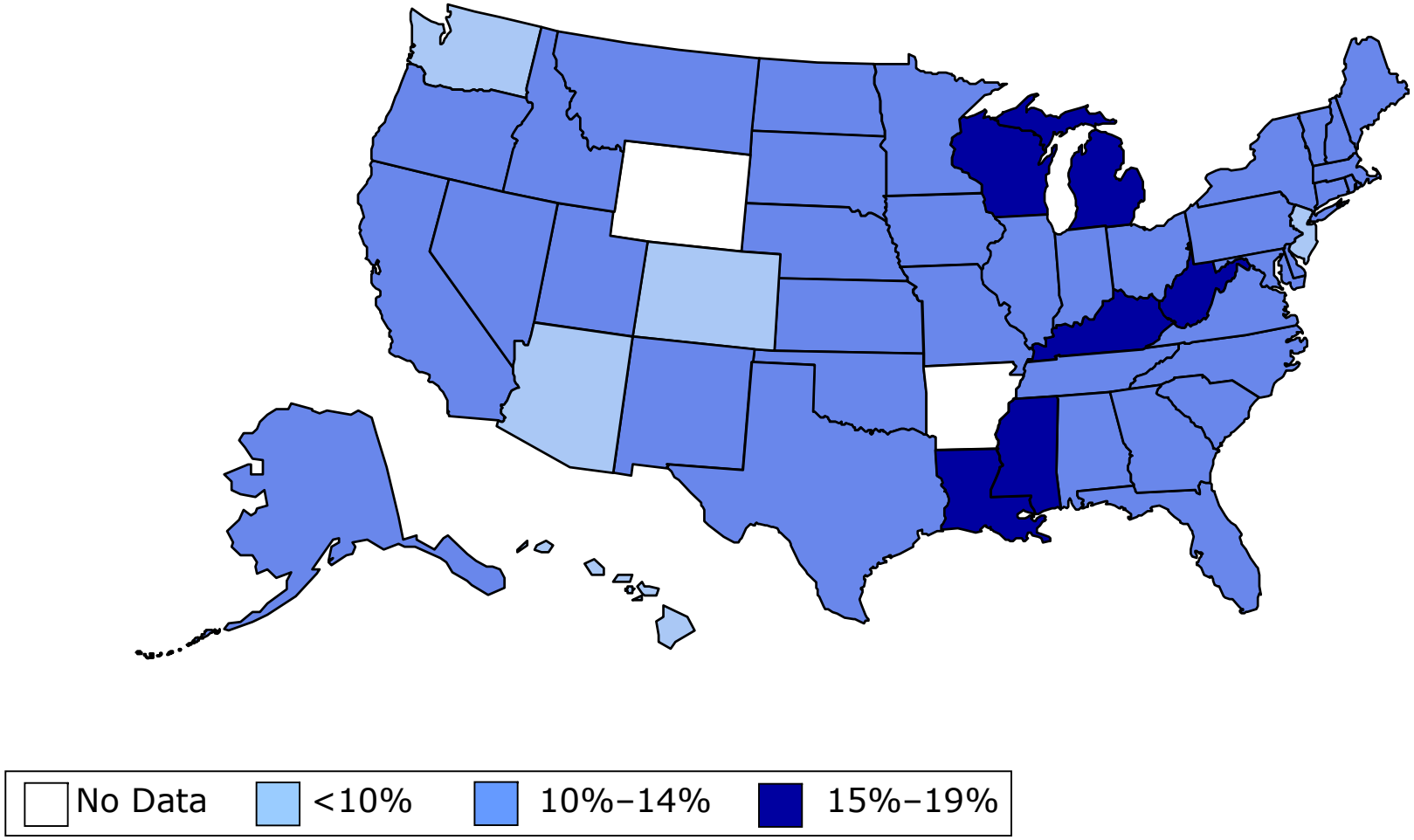
(*BMI ≥30, or ~ 30 lbs overweight for 5’ 4” woman)



Obesity Trends* Among U.S. Adults

BRFSS, 1992

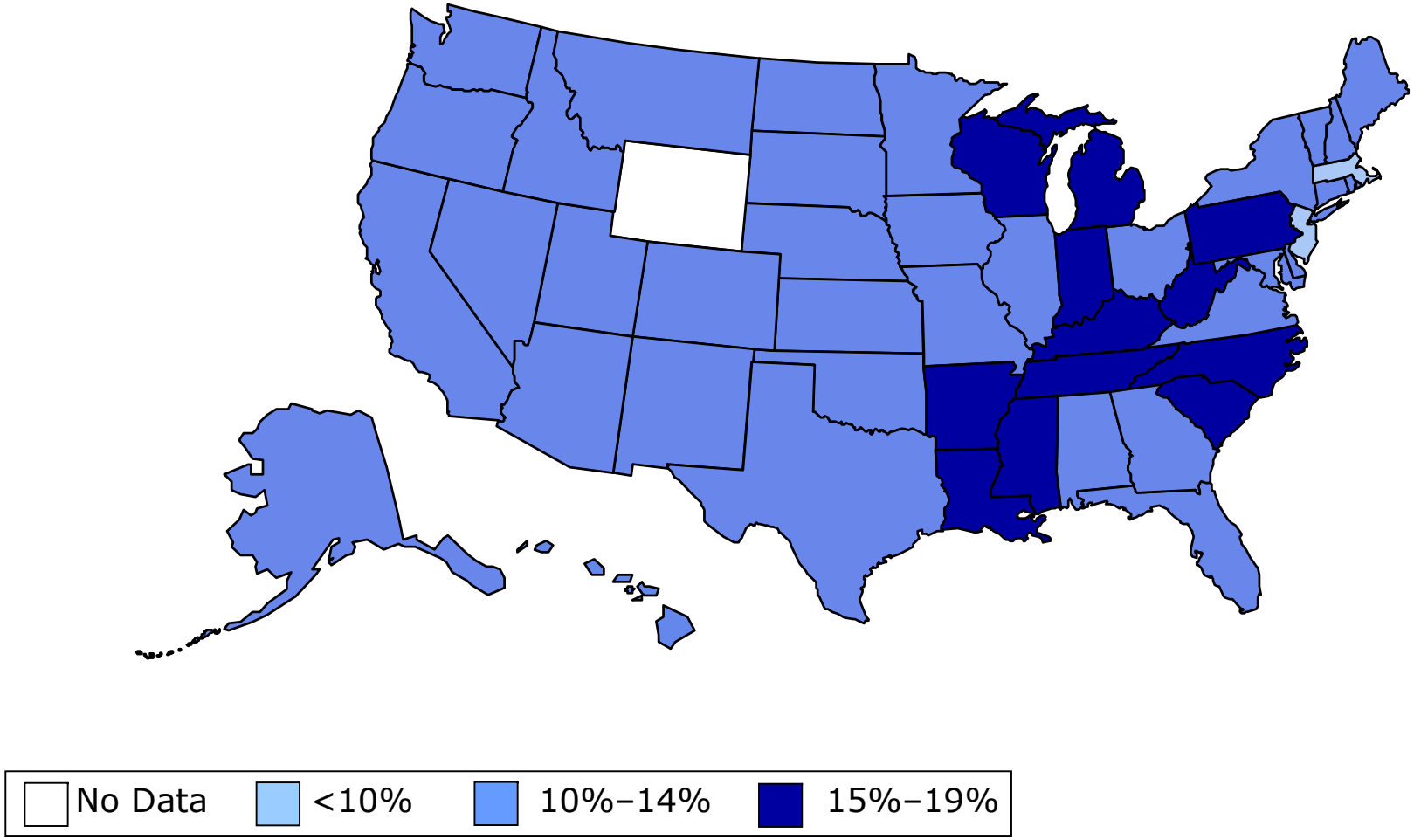
(*BMI ≥30, or ~ 30 lbs overweight for 5’ 4” woman)



Obesity Trends* Among U.S. Adults

BRFSS, 1993

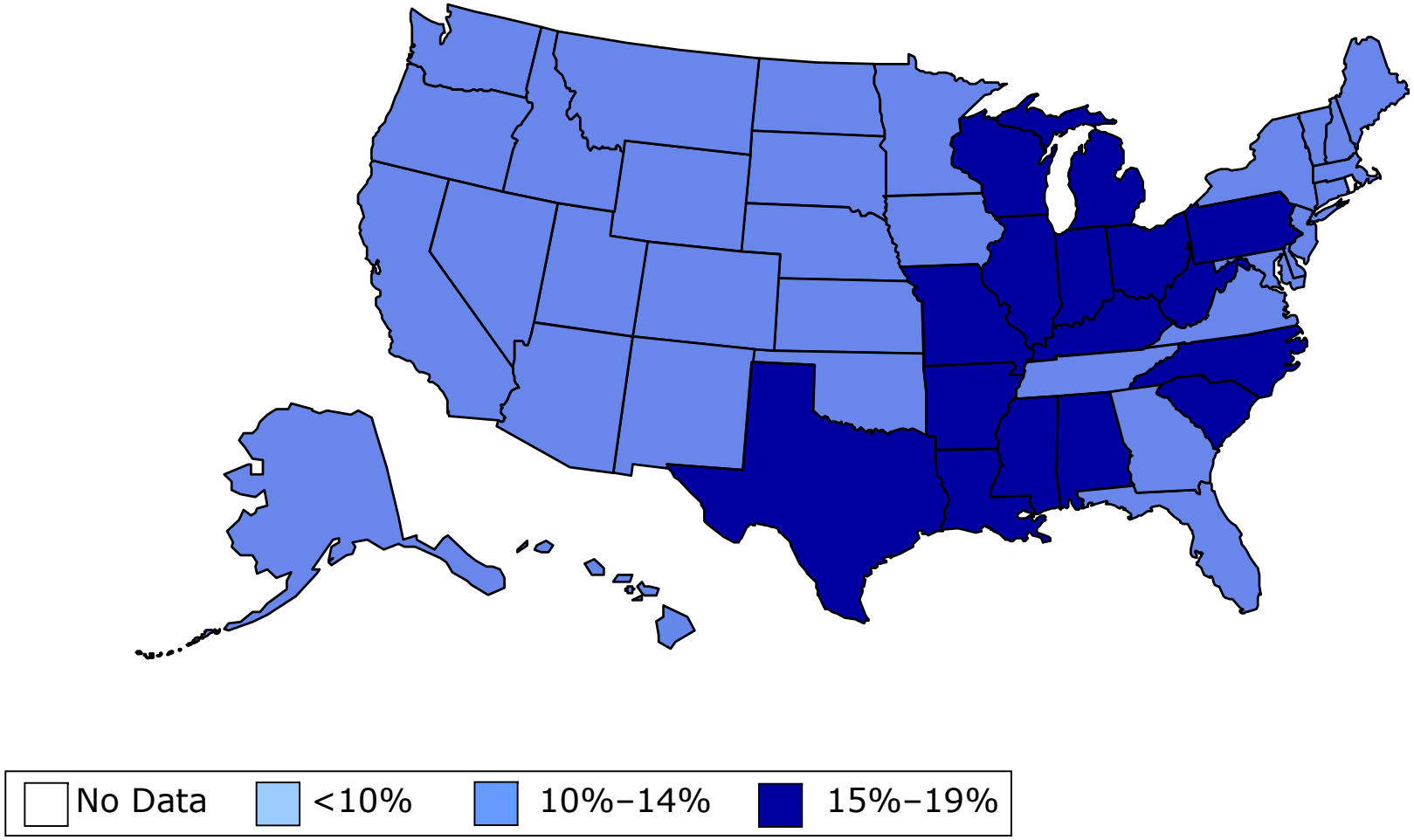
(*BMI ≥30, or ~ 30 lbs overweight for 5’ 4” woman)



Obesity Trends* Among U.S. Adults

BRFSS, 1994

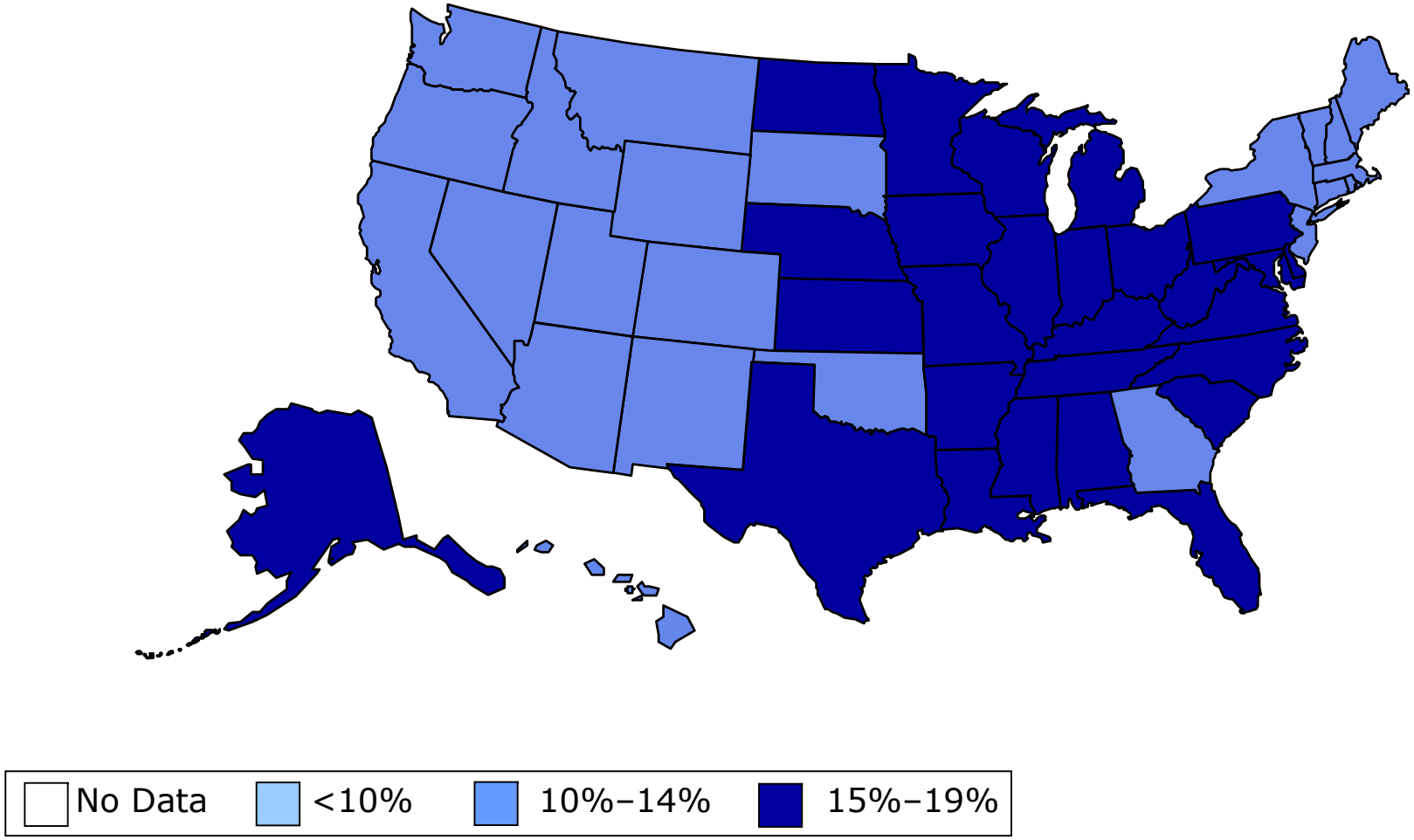
(*BMI ≥30, or ~ 30 lbs overweight for 5’ 4” woman)



Obesity Trends* Among U.S. Adults

BRFSS, 1995

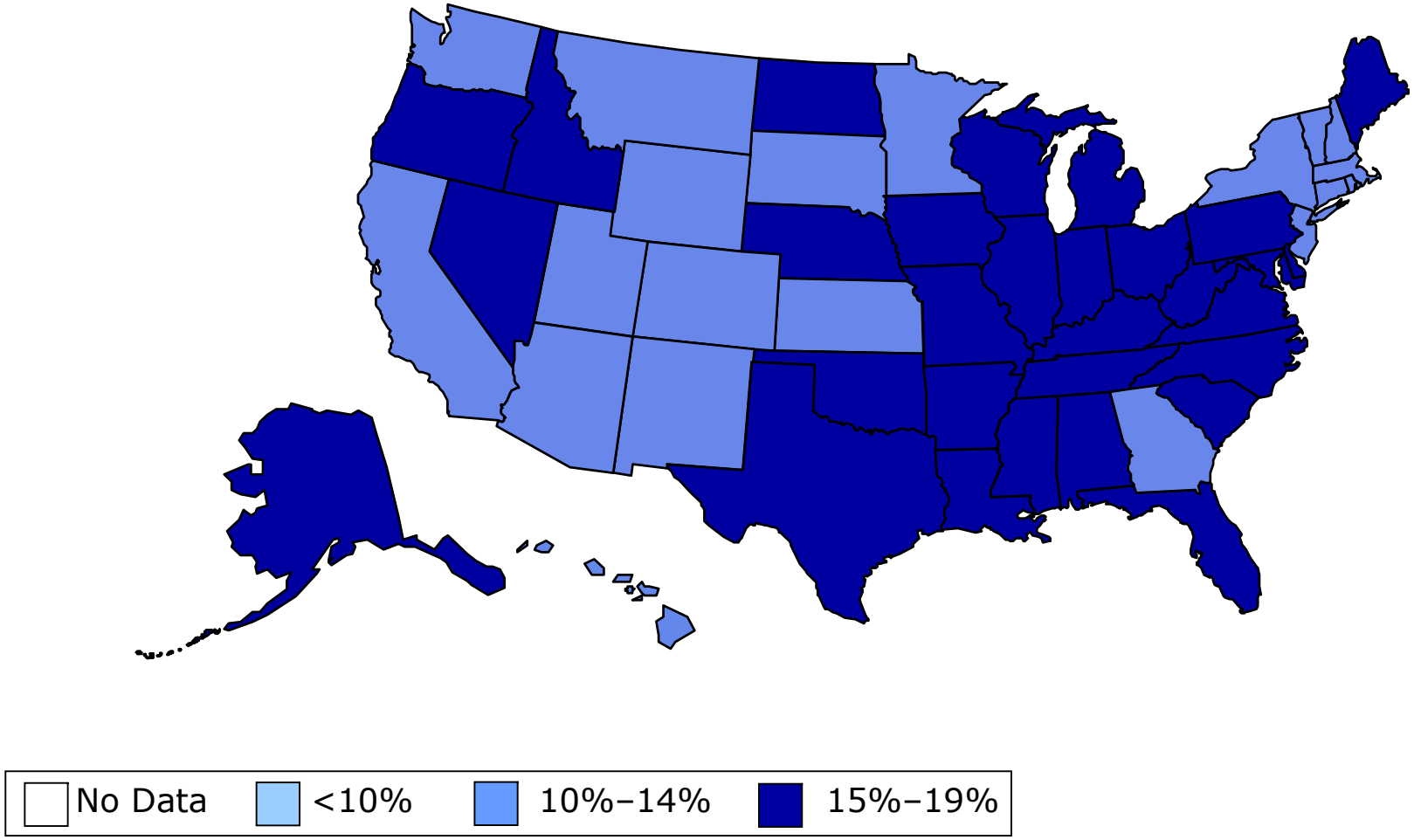
(*BMI ≥30, or ~ 30 lbs overweight for 5’ 4” woman)



Obesity Trends* Among U.S. Adults

BRFSS, 1996

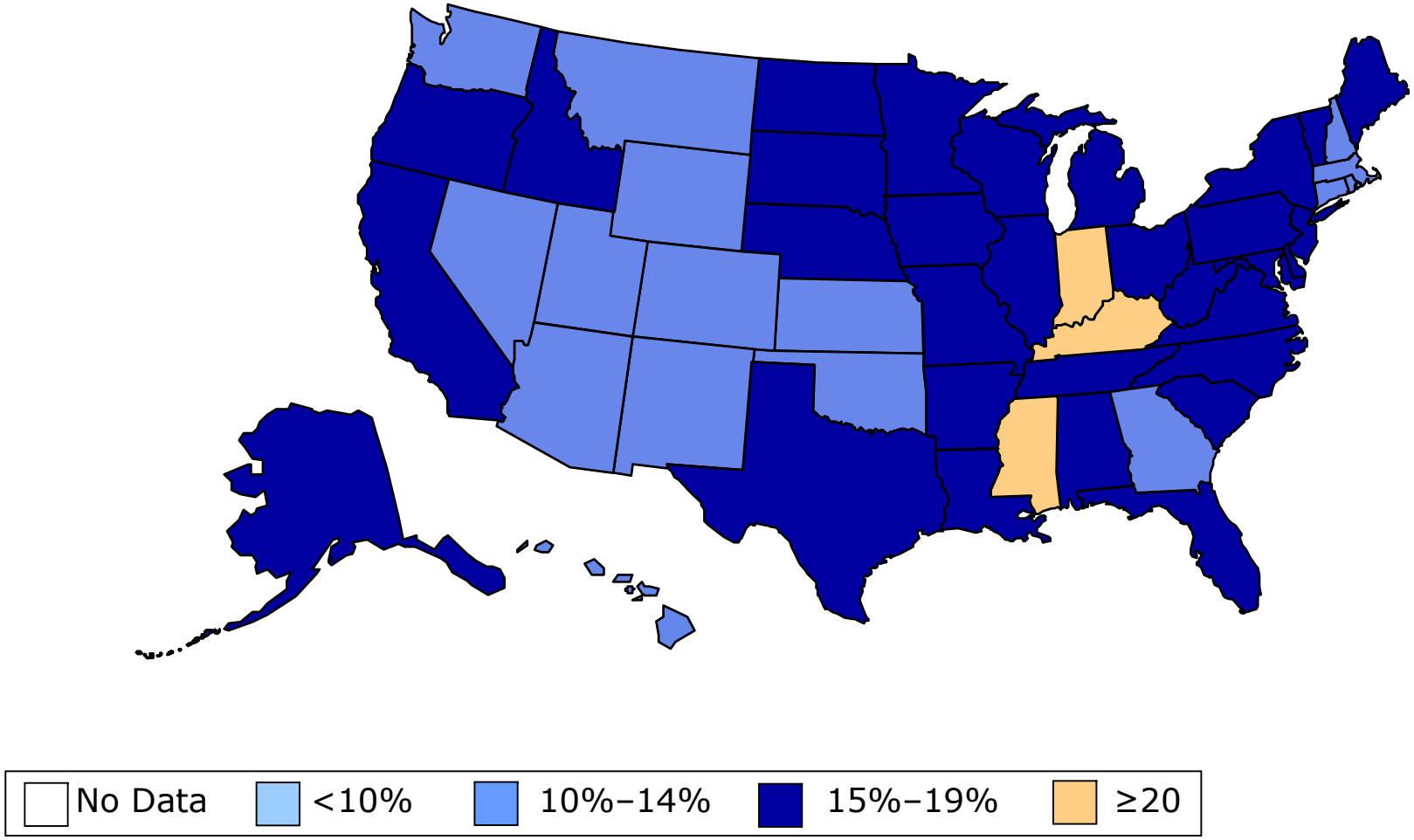
(*BMI ≥30, or ~ 30 lbs overweight for 5’ 4” woman)



Obesity Trends* Among U.S. Adults

BRFSS, 1997

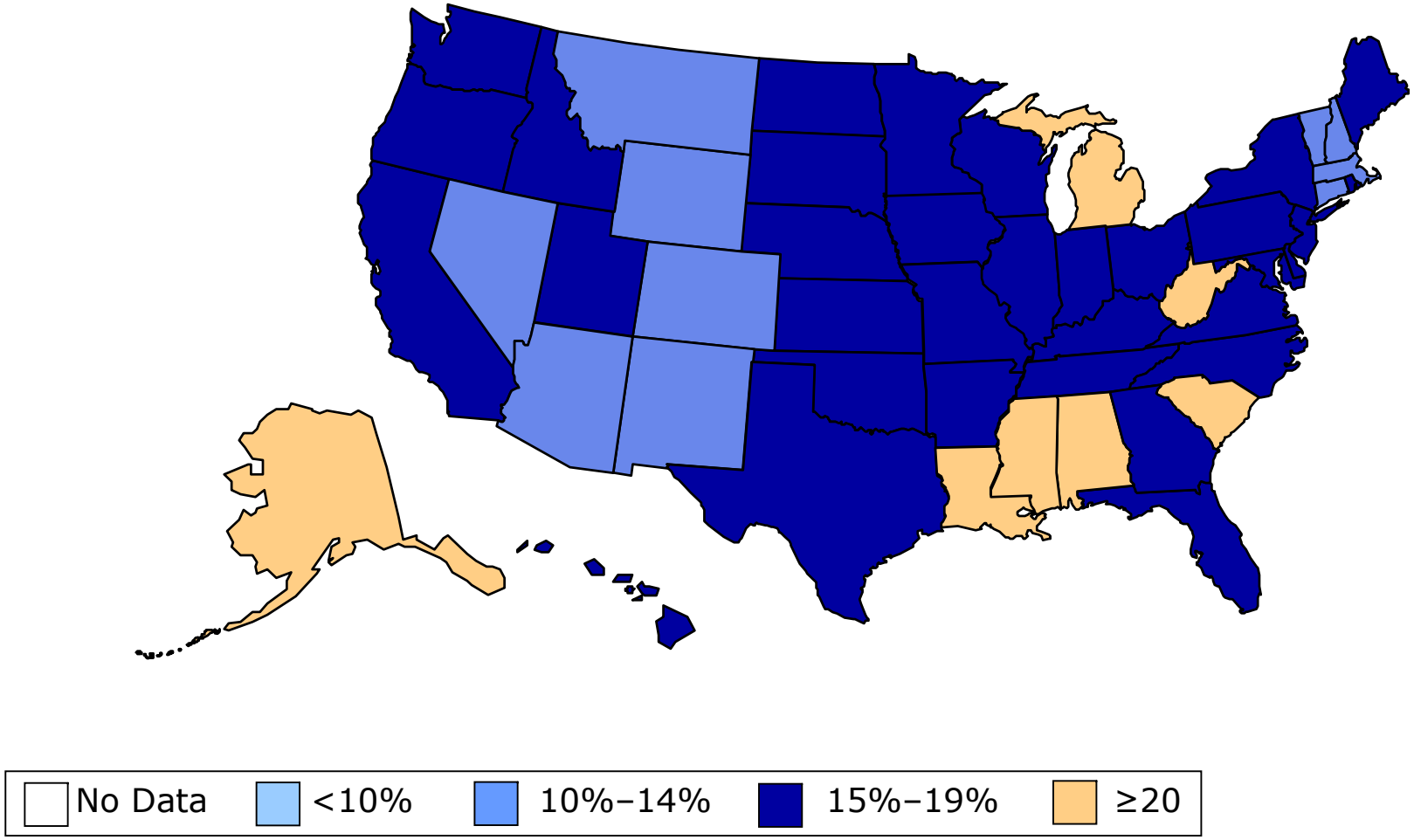
(*BMI ≥30, or ~ 30 lbs overweight for 5’ 4” woman)



Obesity Trends* Among U.S. Adults

BRFSS, 1998

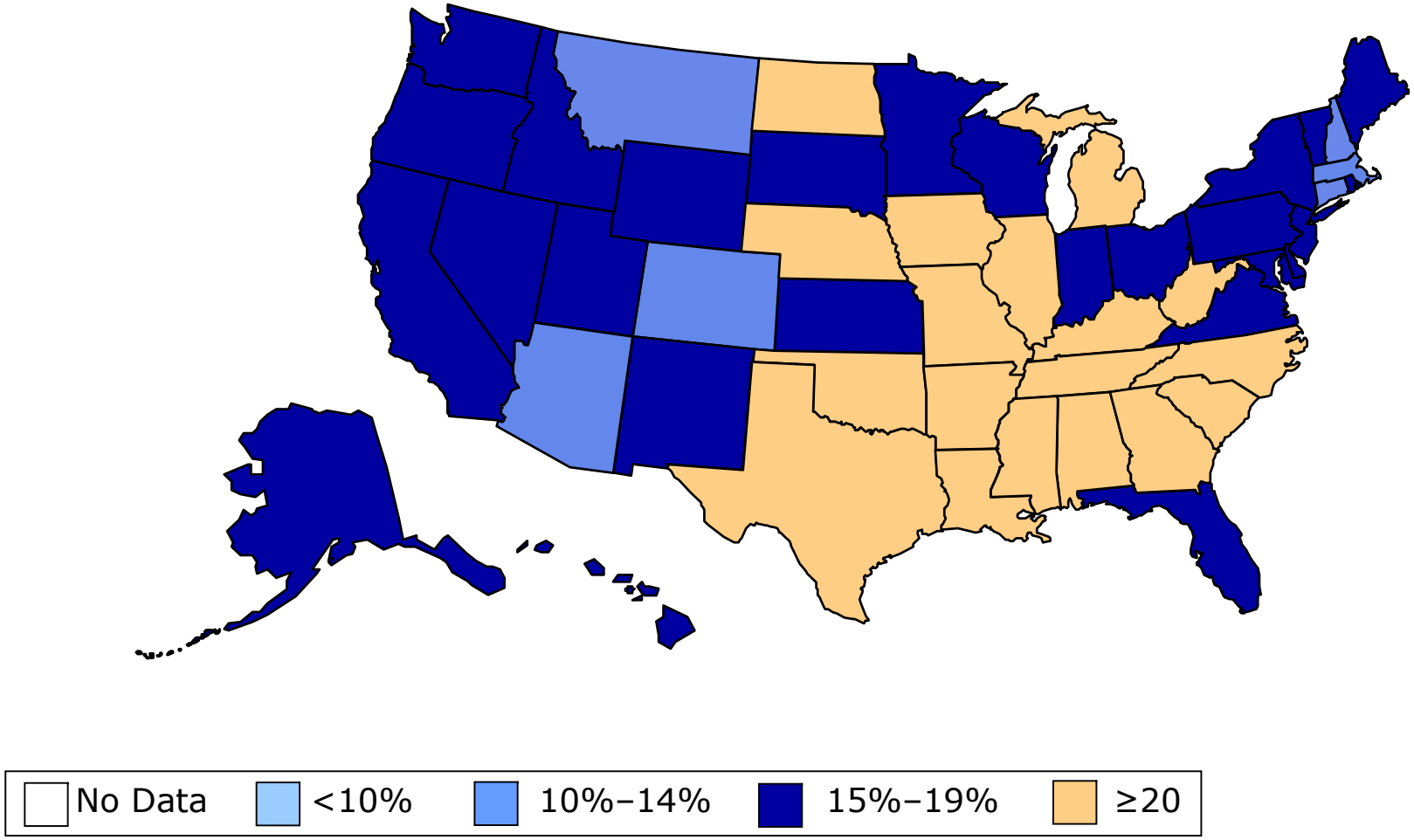
(*BMI ≥30, or ~ 30 lbs overweight for 5’ 4” woman)



Obesity Trends* Among U.S. Adults

BRFSS, 1999

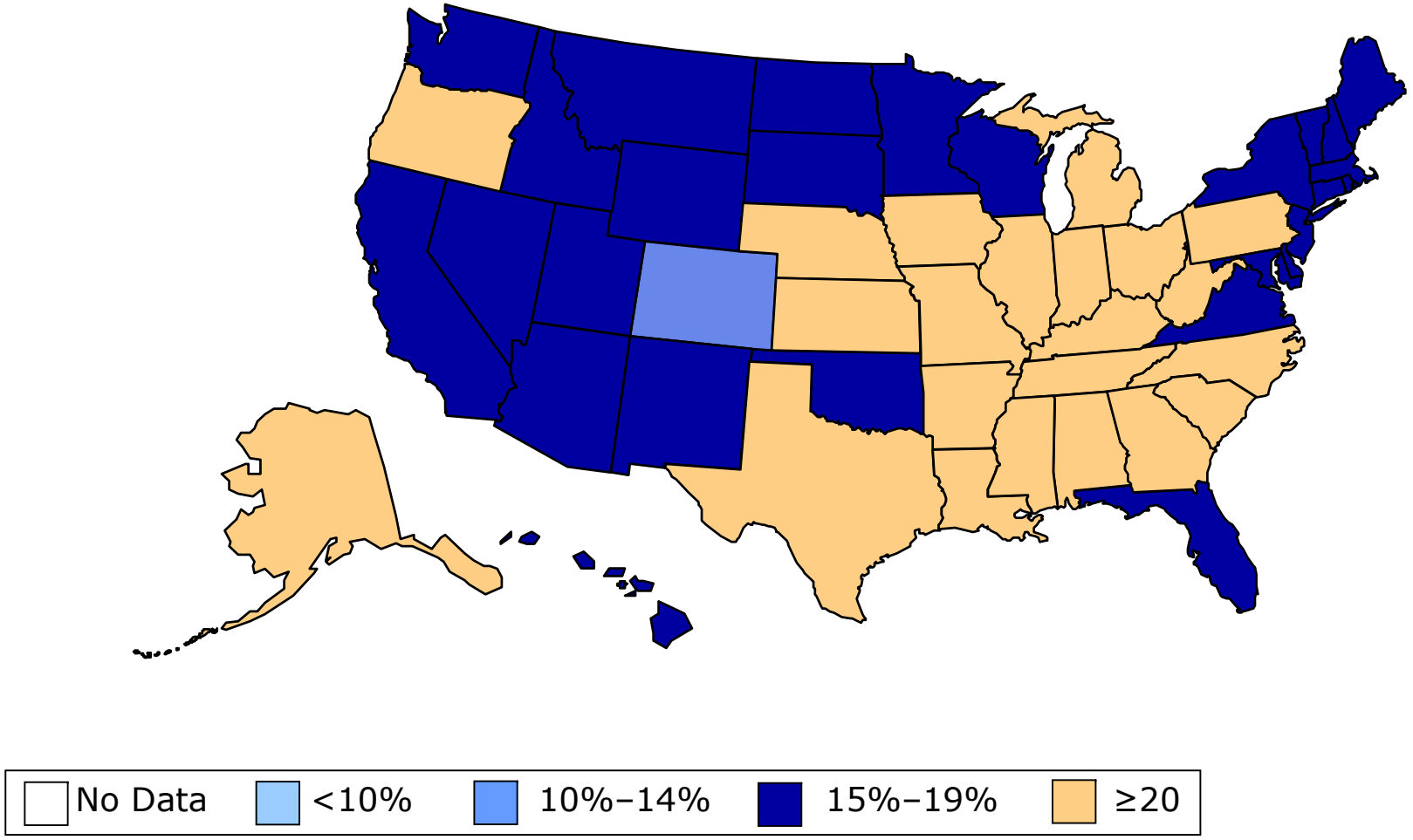
(*BMI ≥30, or ~ 30 lbs overweight for 5’ 4” woman)



Obesity Trends* Among U.S. Adults

BRFSS, 2000

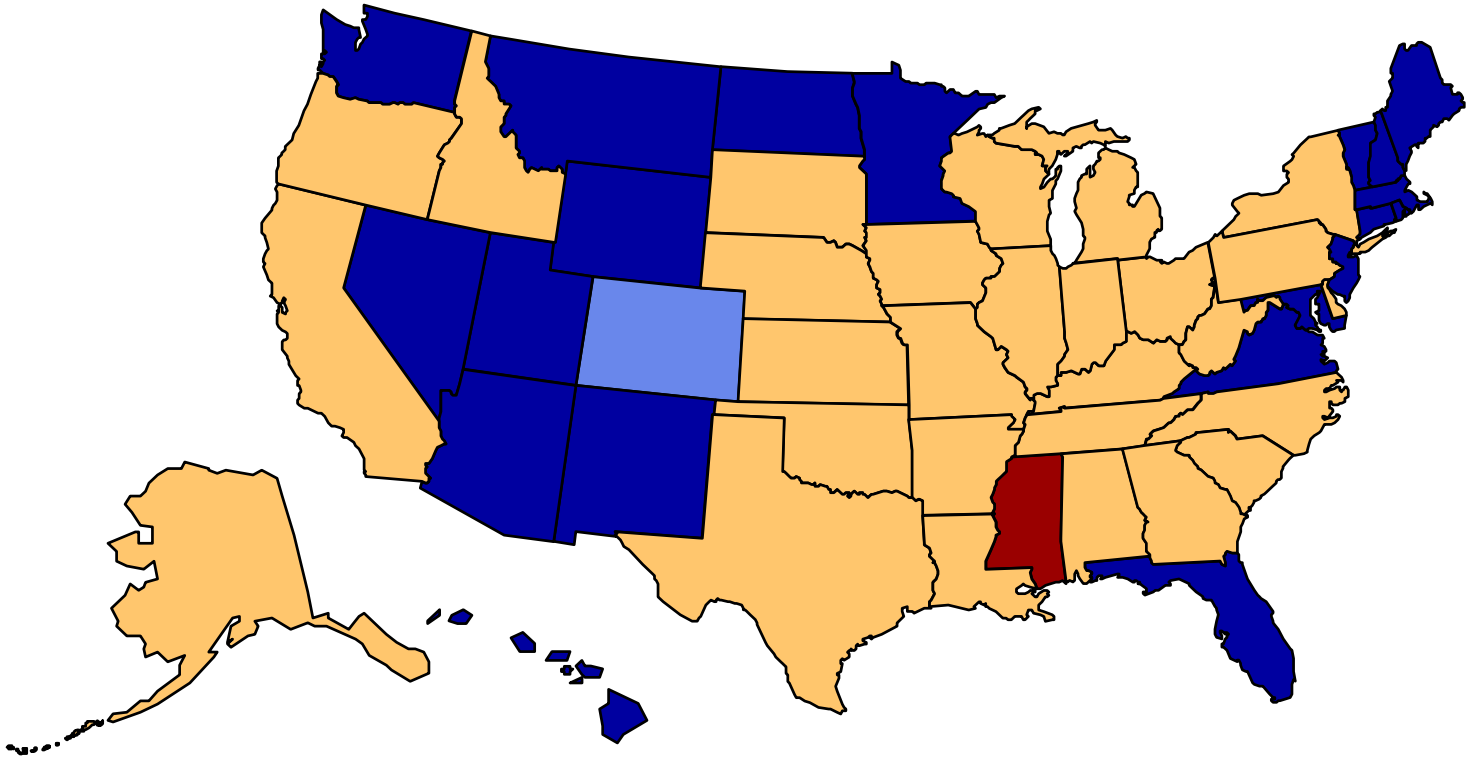
(*BMI ≥30, or ~ 30 lbs overweight for 5’ 4” woman)



Obesity Trends* Among U.S. Adults

BRFSS, 2001

(*BMI ≥30, or ~ 30 lbs overweight for 5’ 4” woman)

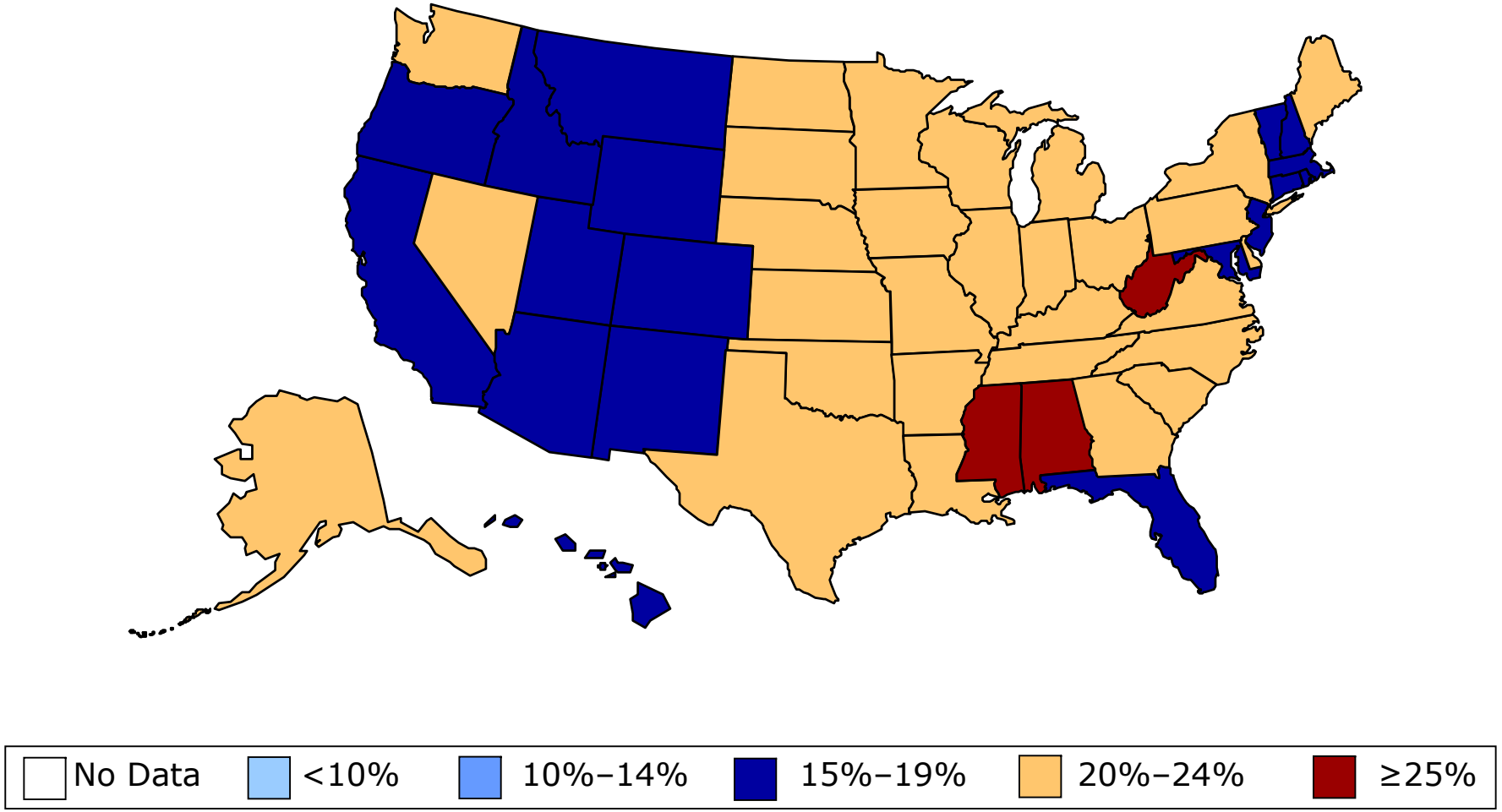


No Data | <10% | 10%–14% | 15%–19% | 20%–24% | ≥25%

Obesity Trends* Among U.S. Adults

BRFSS, 2002

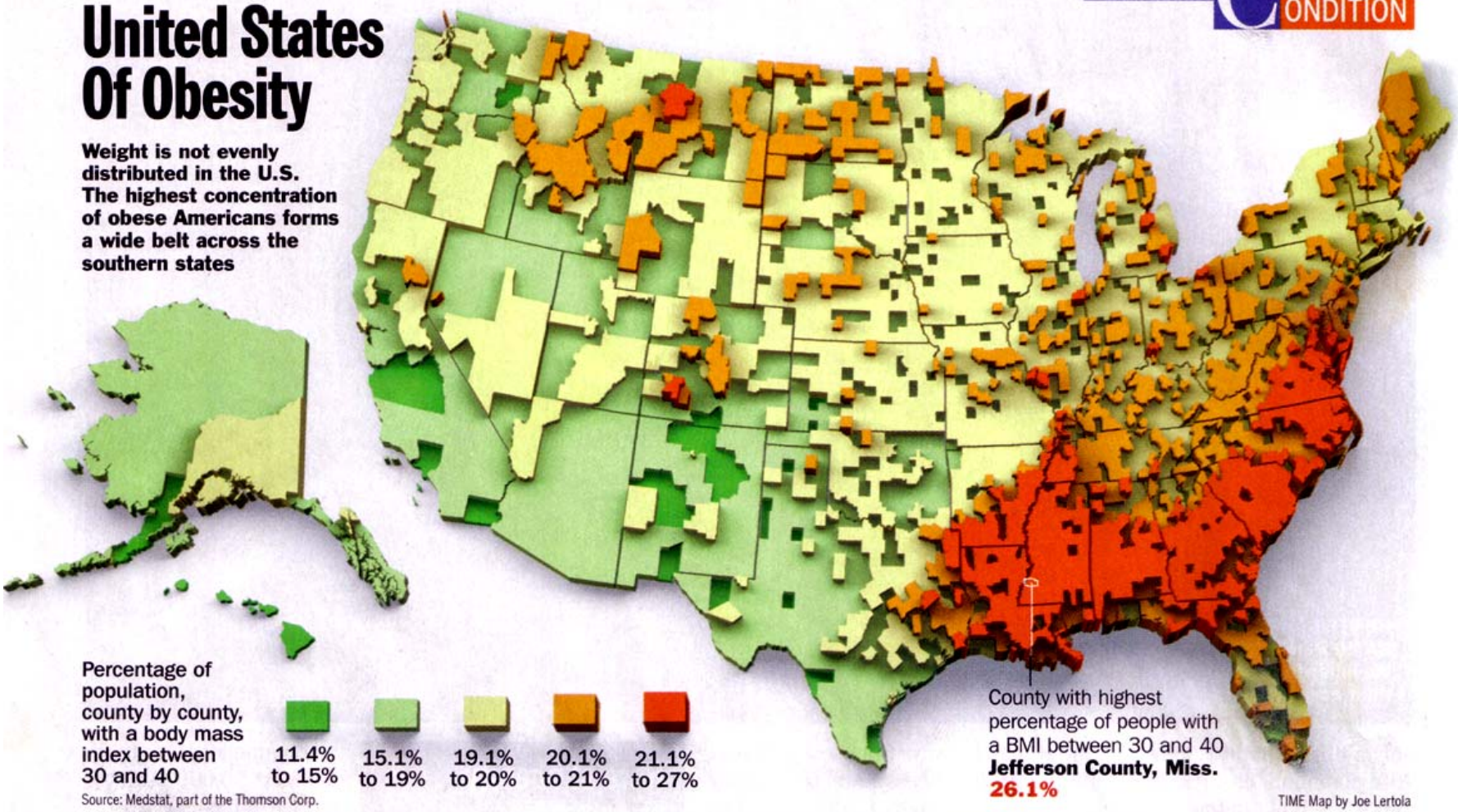
(*BMI ≥30, or ~ 30 lbs overweight for 5’ 4” woman)



Source: Behavioral Risk Factor Surveillance System, CDC

United States Of Obesity

Weight is not evenly distributed in the U.S. The highest concentration of obese Americans forms a wide belt across the southern states



Source: Medstat, part of the Thomson Corp.

TIME Map by Joe Lertola

WHAT IS BMI?

$$\frac{\text{weight in pounds}}{(\text{height in inches})^2} \times 703$$

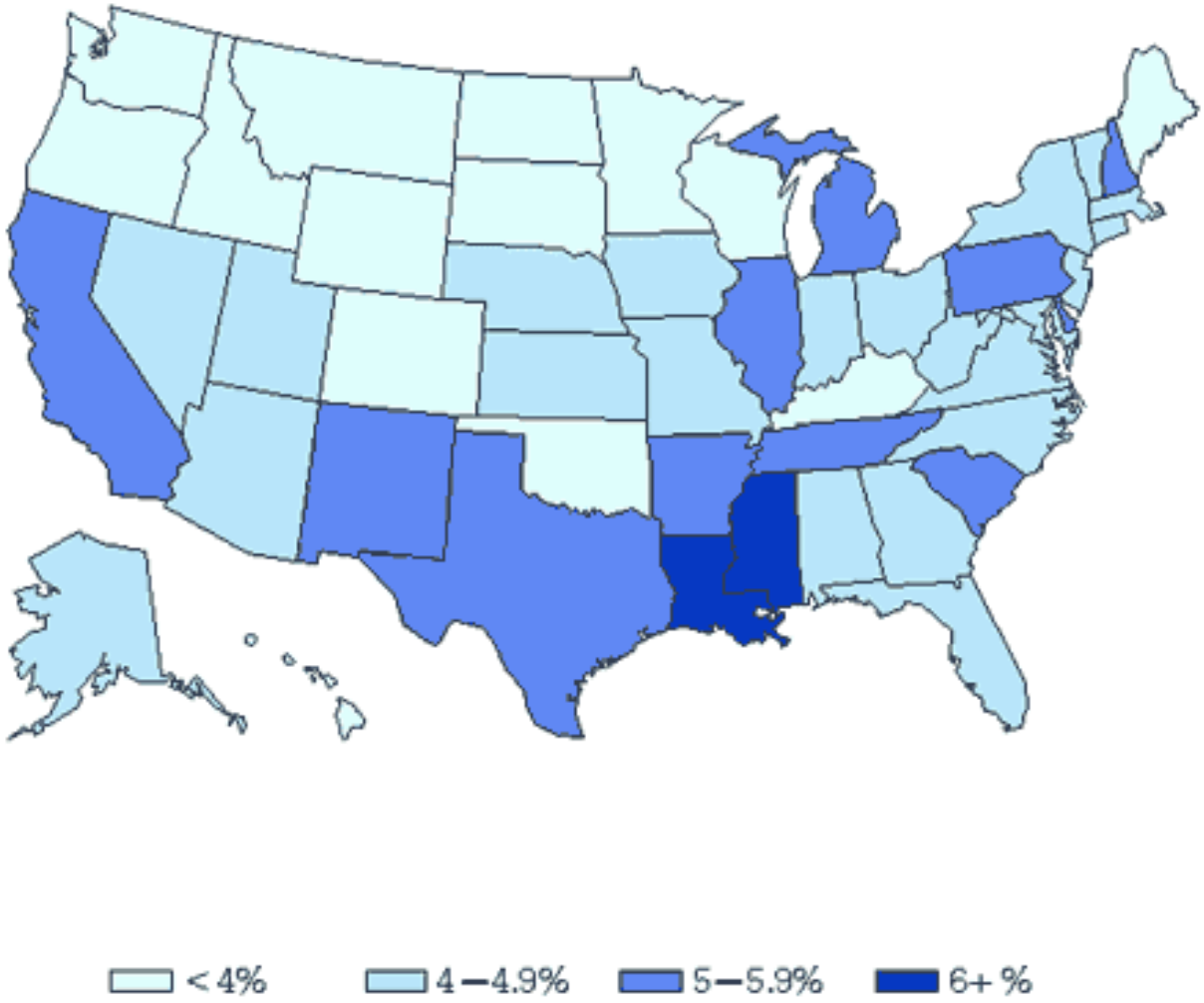
EXAMPLE:

$$\text{weight} = \frac{160 \text{ lbs.}}{(69 \text{ in.})^2} \times 703 = 23.6 \text{ BMI}$$

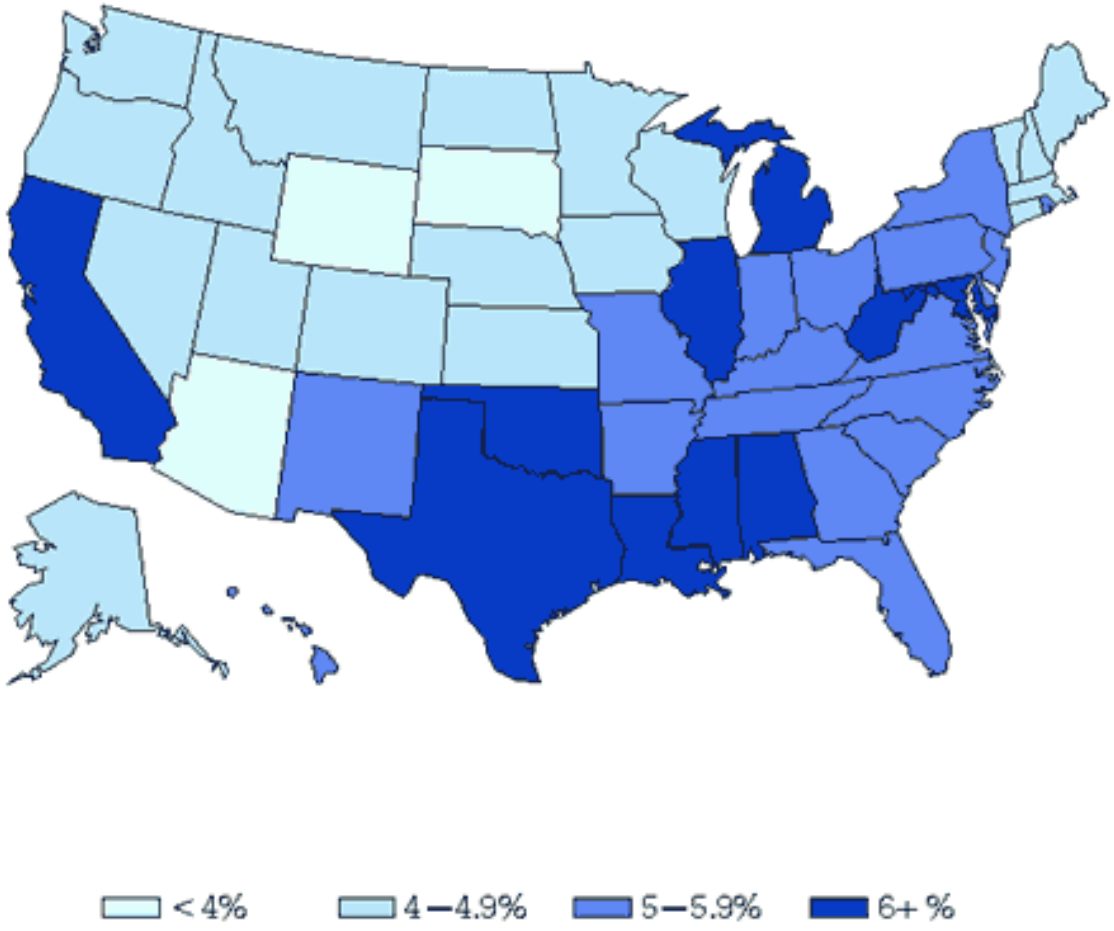
Body mass index is a more accurate measurement than weight because it takes into account that short people tend to weigh less than tall people. It's not perfect, however. The BMI of highly muscular athletes is often in the obese range.

BMI	STATUS
Below 18.5	Underweight
18.5-24.9	Normal
25.0-29.9	Overweight
30.0-39.9	Obese
40 and above	Morbidly obese

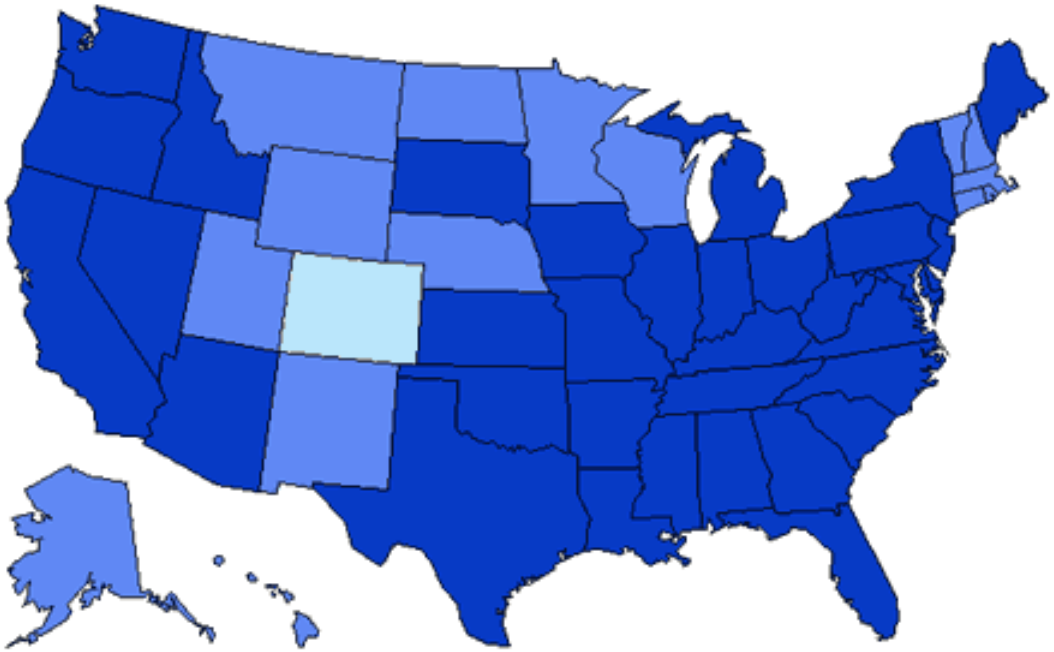
Diabetes prevalence 1994



Diabetes prevalence 1998

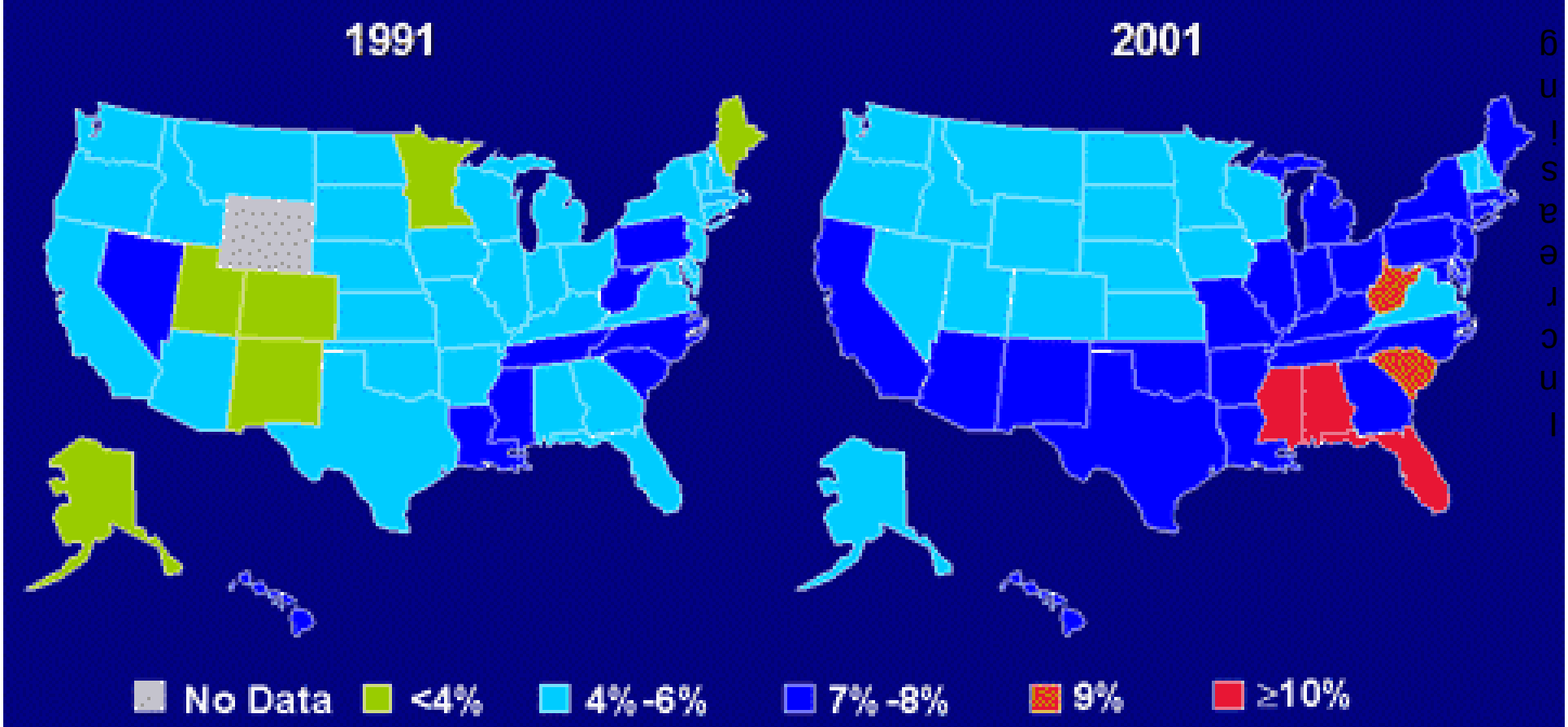


Diabetes prevalence 2003



In 2002: 18.2 million people, or 6.3%

Increasing Prevalence of Diagnosed Diabetes in US Adults

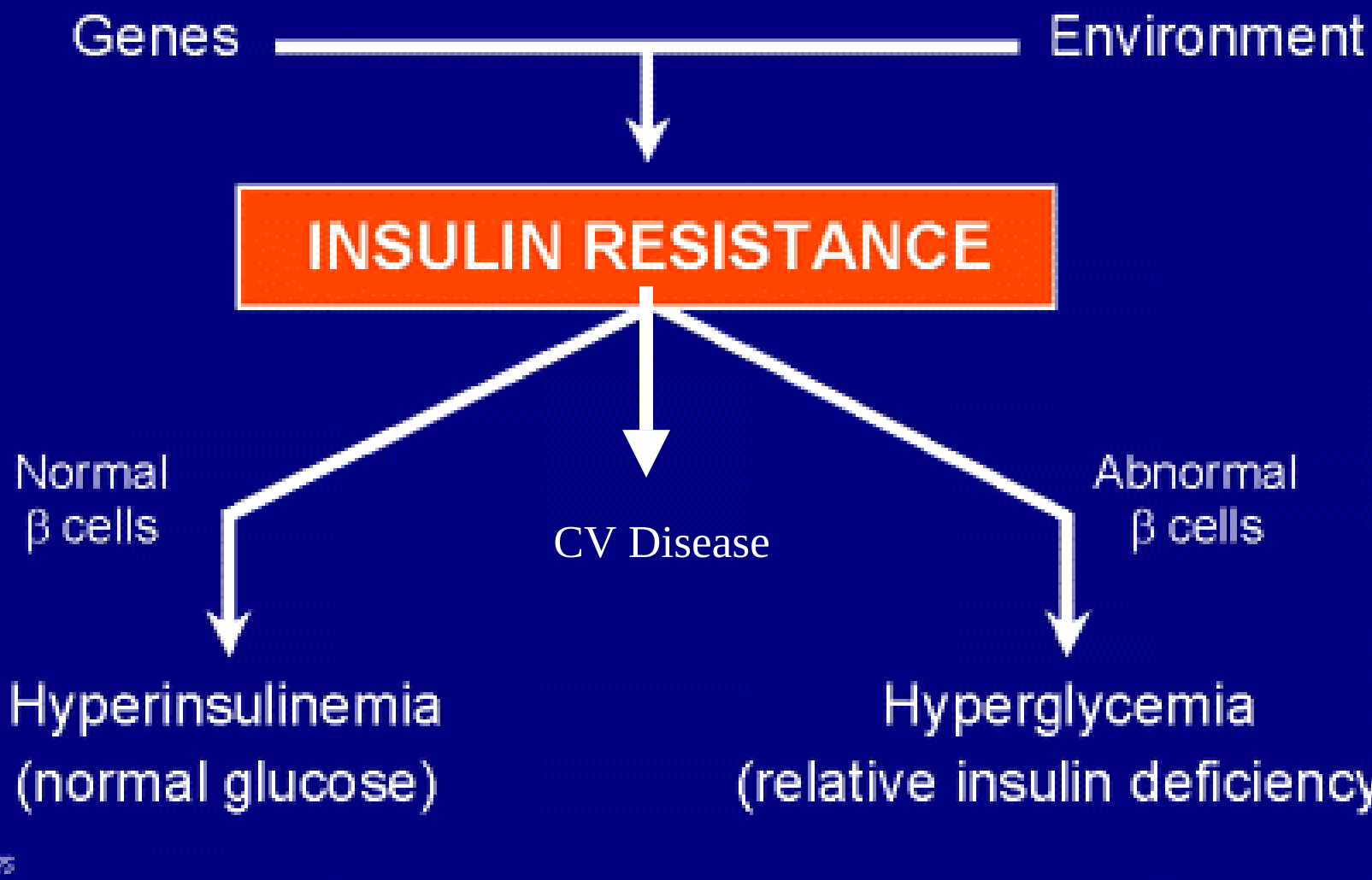


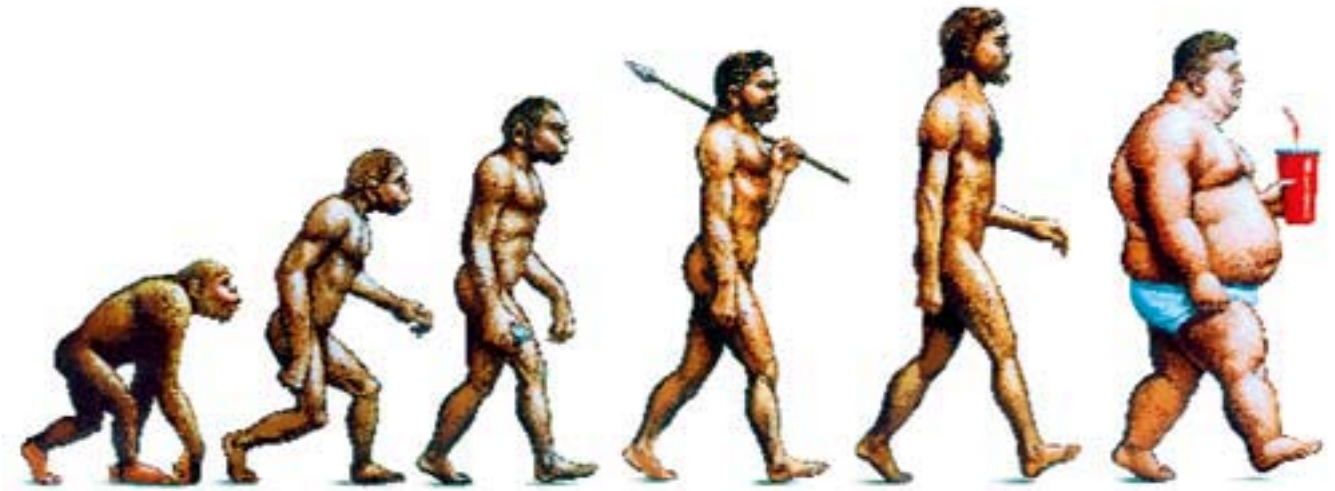
Mokdad AH et al. *JAMA*. 2003;289:76-79.

What causes metabolic syndrome?

- Genetic predisposition
- Ethnicity
- Lifestyle and culture of inactivity and obesity
- Aging

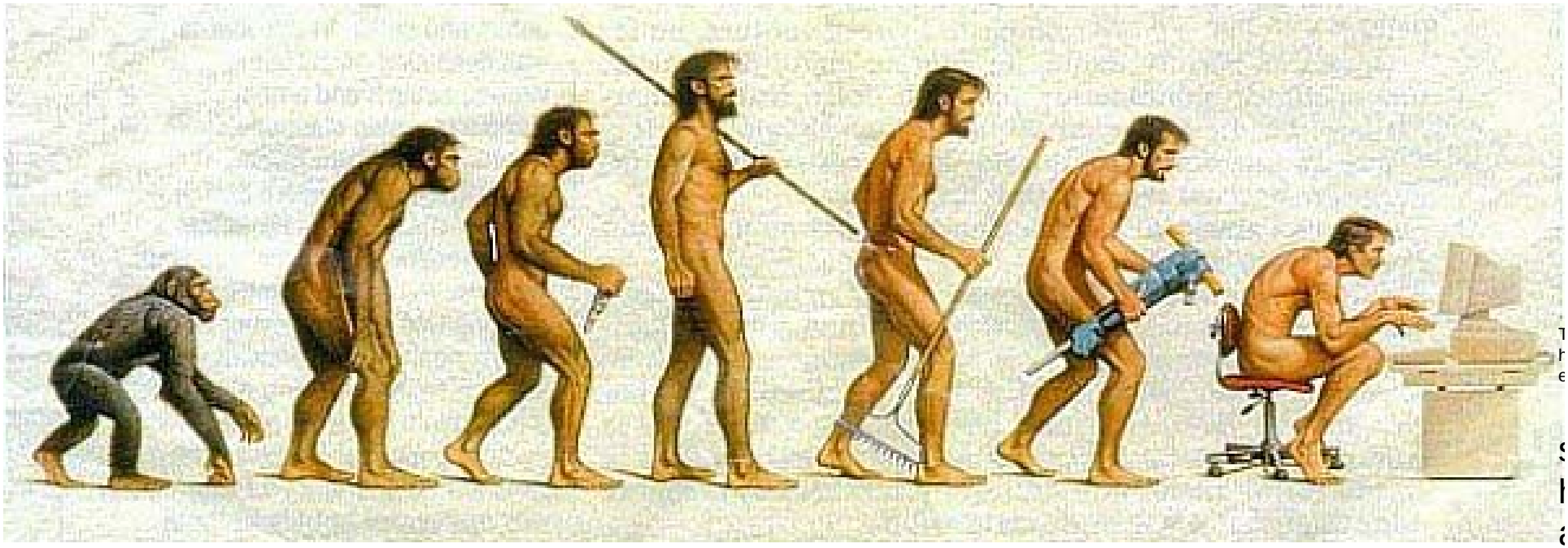
Response to Insulin Resistance: The Pancreatic β Cell





The shape of t

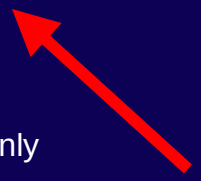
Economist Dec 2003



NCEP ATP III:
Working Definition of the Metabolic Syndrome

≥3 of the following:

Risk Factor	Defining Level
Abdominal obesity (waist circumference*)	
Men	>102 cm (>40 in)
Women	> 88 cm (>35 in)
Triglycerides	≥150 mg/dL
HDL cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/≥85 mm Hg
Fasting glucose	≥110 mg/dL



*Some male patients may develop multiple metabolic risk factors when waist circumference is only marginally increased (eg, 94–102 cm [37–40 inches]).

NCEP ATP III. *JAMA*. 2001;285:2486–2495.

METABOLIC SYNDROME DEFINITION

- NCEP ATP 3

At least three of the following:

- Prediabetes or diabetes
- Hypertension (>130/85)
- High triglycerides >150
- Low HDL cholesterol
  men <40, women <50
- Obesity
  waist circumference >40in. men
  waist circumference >35in. women

- WHO

- Diabetes, prediabetes, or insulin resistance

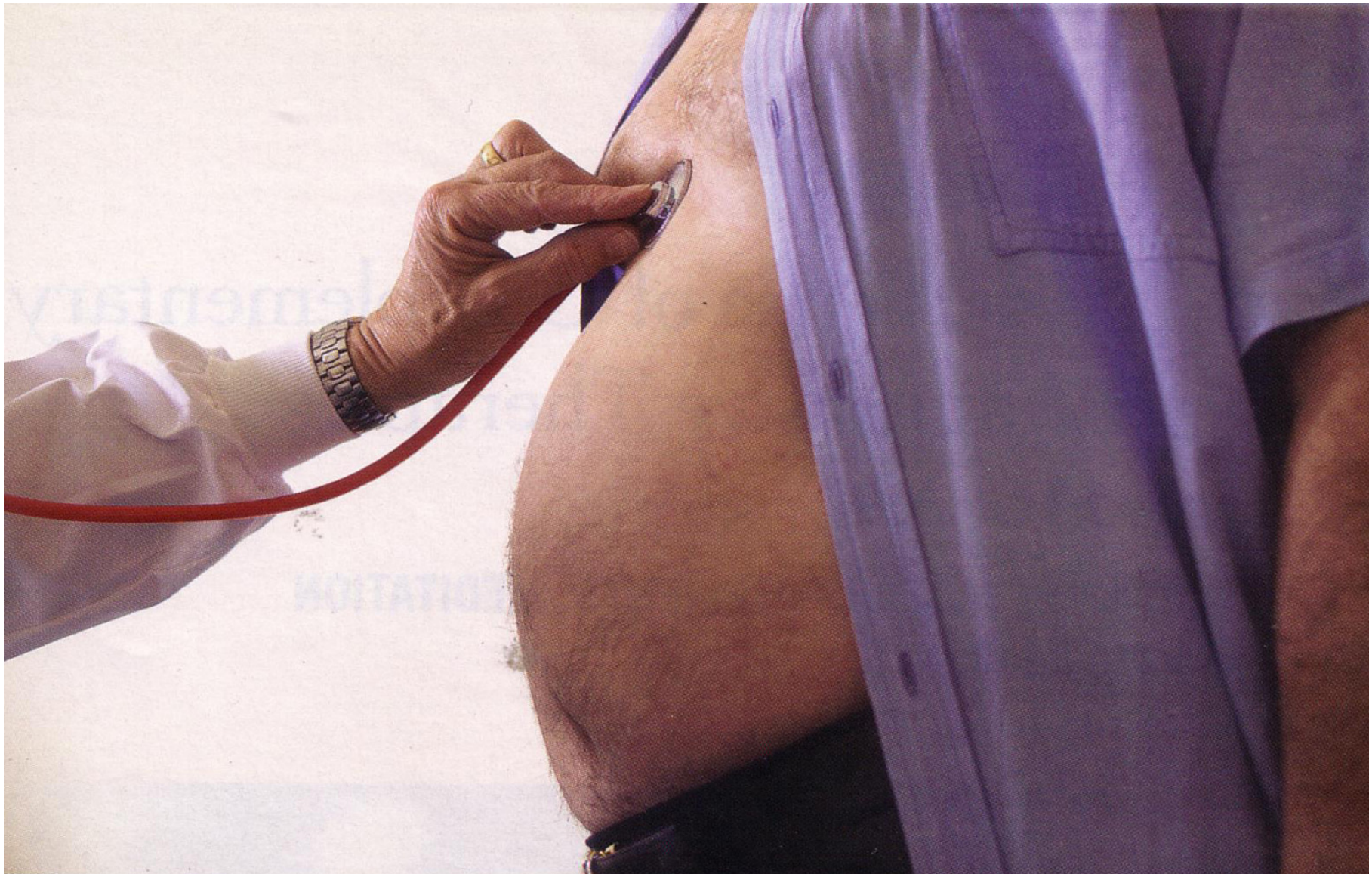
Plus any two of the following:

- hypertension (>140/90 or Rx)
- high triglycerides >150
- low HDL cholesterol
  <35 men, <40 women
- obesity (BMI >30)
- increase urine albumin

Measuring Insulin Sensitivity

- Insulin levels ?
- Clamp studies?
- HOMA-IR?

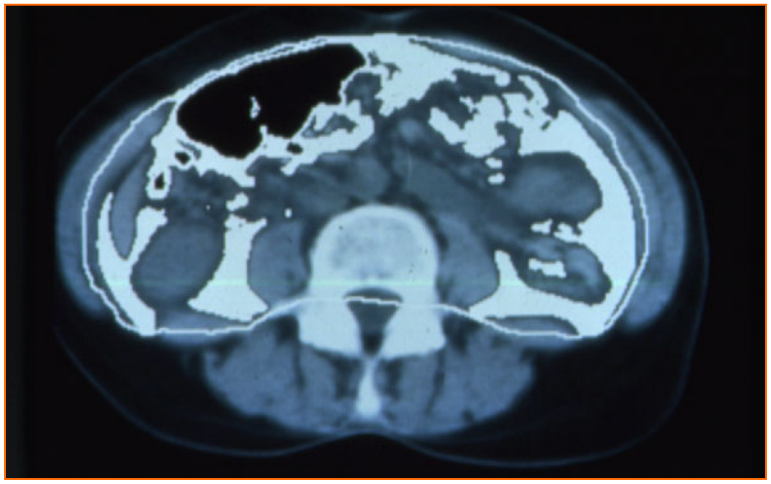
Patterns of Body Fat Distribution

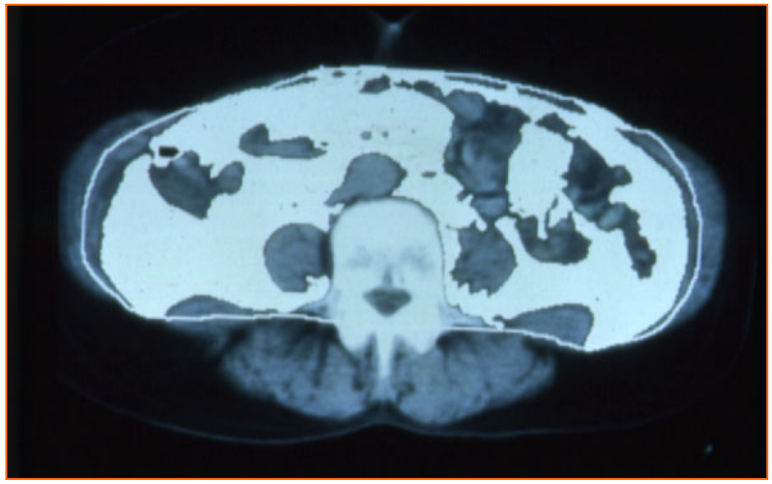


Visceral

Visceral Fat Distribution

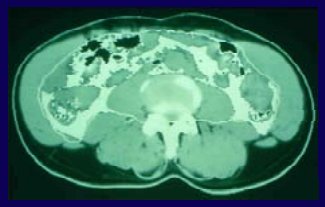
Normal vs Type 2 Diabetes

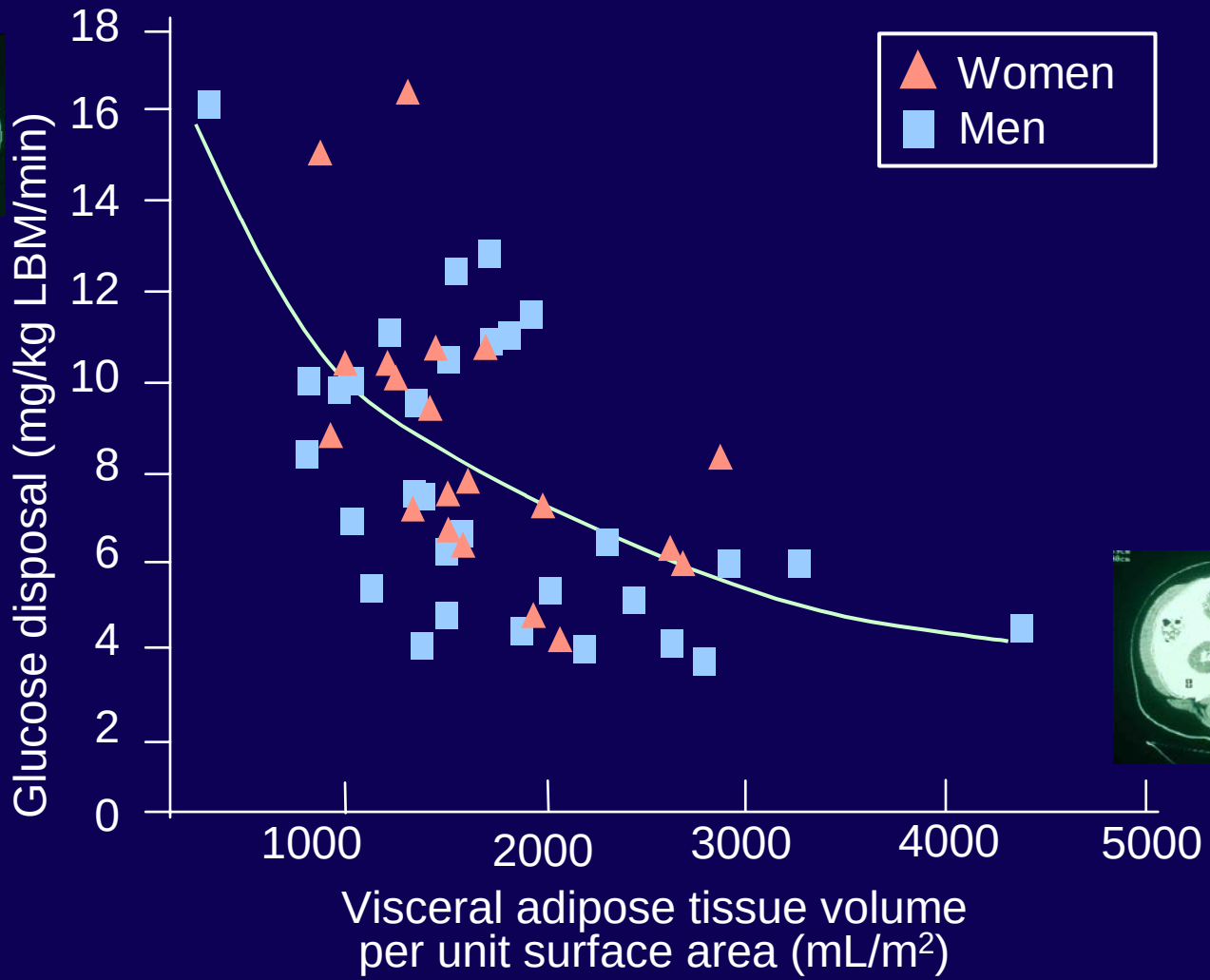




Courtesy of Wilfred Y. Fujimoto, MD.

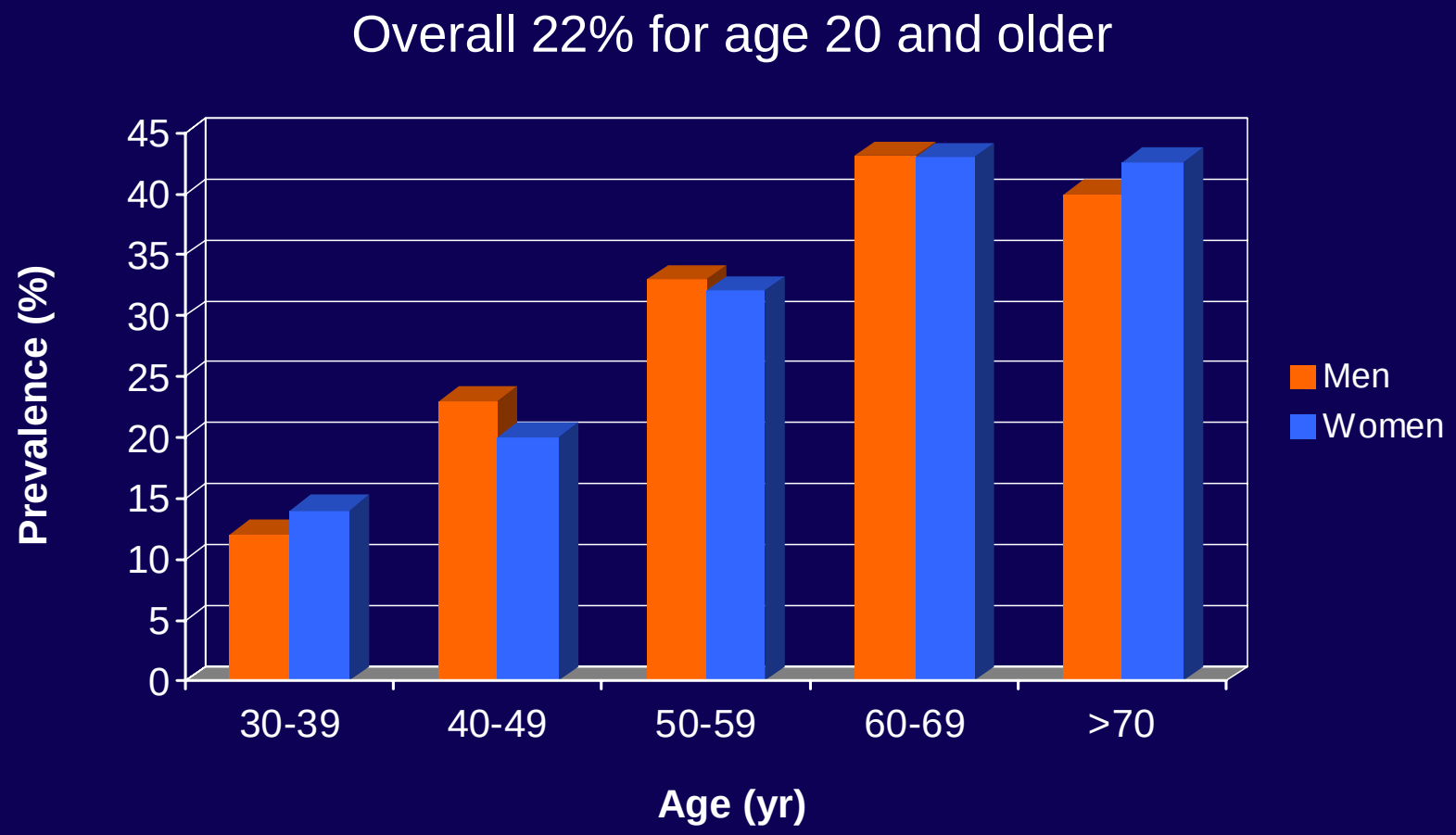
Relationship Between Visceral Adipose Tissue and Insulin Action





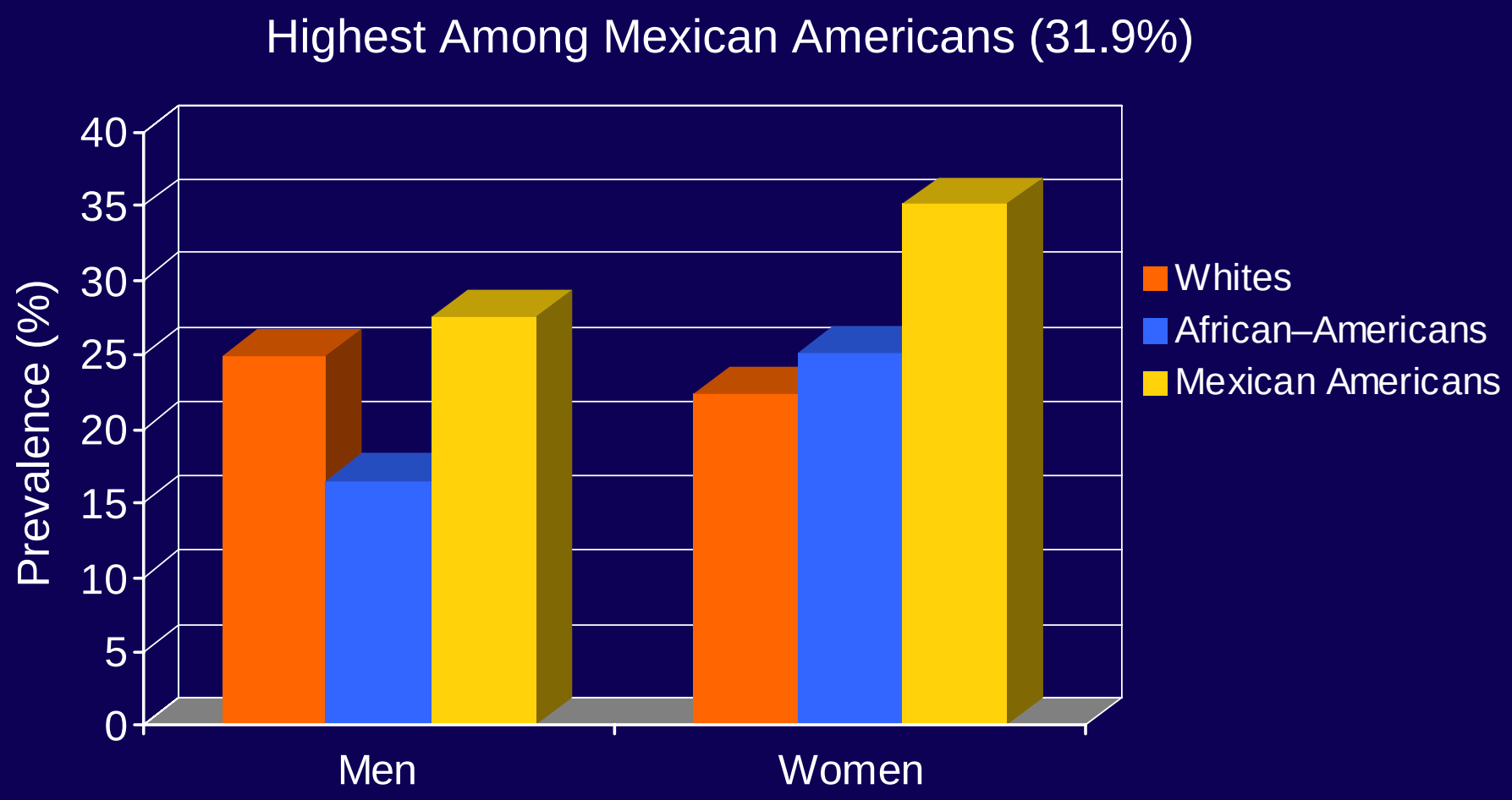
Banerji M et al. *Am J Physiol* 1997;273(2 pt 1):E425–E432.

Prevalence of the Metabolic Syndrome by ATP III Criteria — NHANES III Population



Adapted from: Ford ES et al. *JAMA.* 2002;287:356–359.

Prevalence of the Metabolic Syndrome by ATP III Criteria — NHANES III Population



Adapted from: Ford ES et al. *JAMA.* 2002;287:356–359.

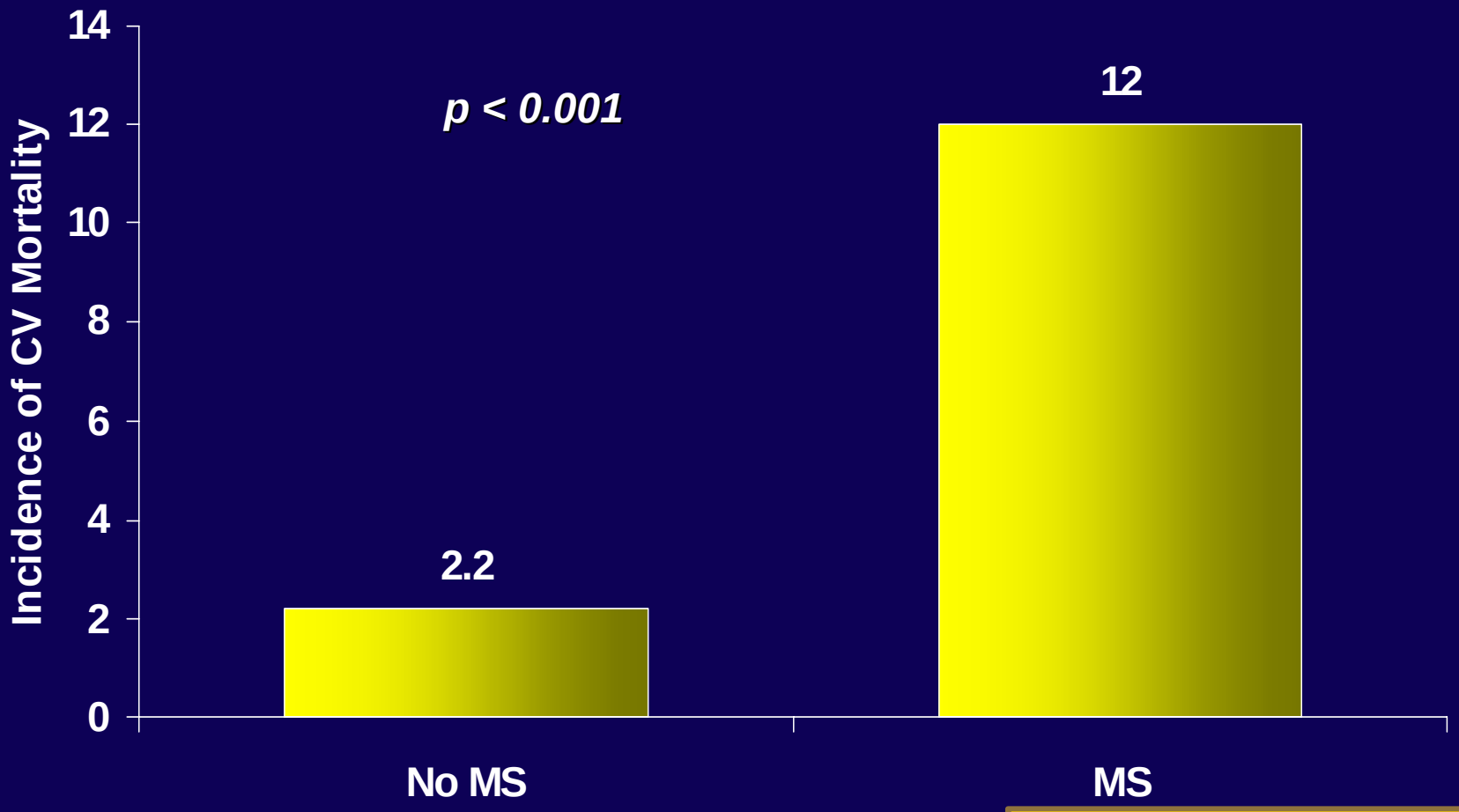
Metabolic Syndrome Leads to Significant Morbidity and Mortality

- In an epidemiological study (N = 4483), patients with metabolic syndrome had, compared with normal patients, a relative risk of
  - 2.96 for CHD
  - 2.63 for MI
  - 2.27 for stroke
  - 1.81 for death (median follow-up of 6.9 years)

Isomaa B, et al. *Diabetes Care*. 2001;24:683-689.

Morbidity and mortality

Cardiovascular Mortality Associated With Metabolic Syndrome (MS)



Diabetes Care 2001;24:683

Goals for Managing the Metabolic Syndrome

An opportunity to *prevent* predictable complications:

- Type 2 diabetes
- Cardiovascular events

LIPOTOXICITY

Free fatty acids
cytokines

Chemokines
Adhesion molecules

HYPERTENSION

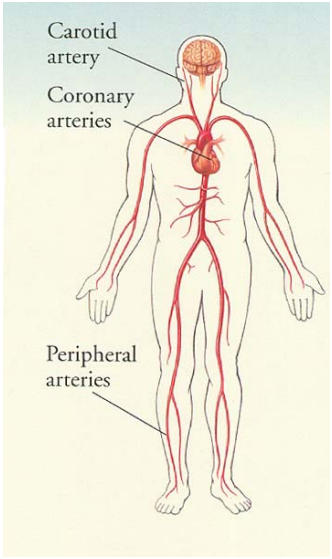
LIPID ABNORMALITIES

INSULIN
RESISTANCE

Beta cell failure

VASCULAR EFFECTS
constriction
inflammation
atherogenesis
procoagulant

STROKE
CAD
PAD



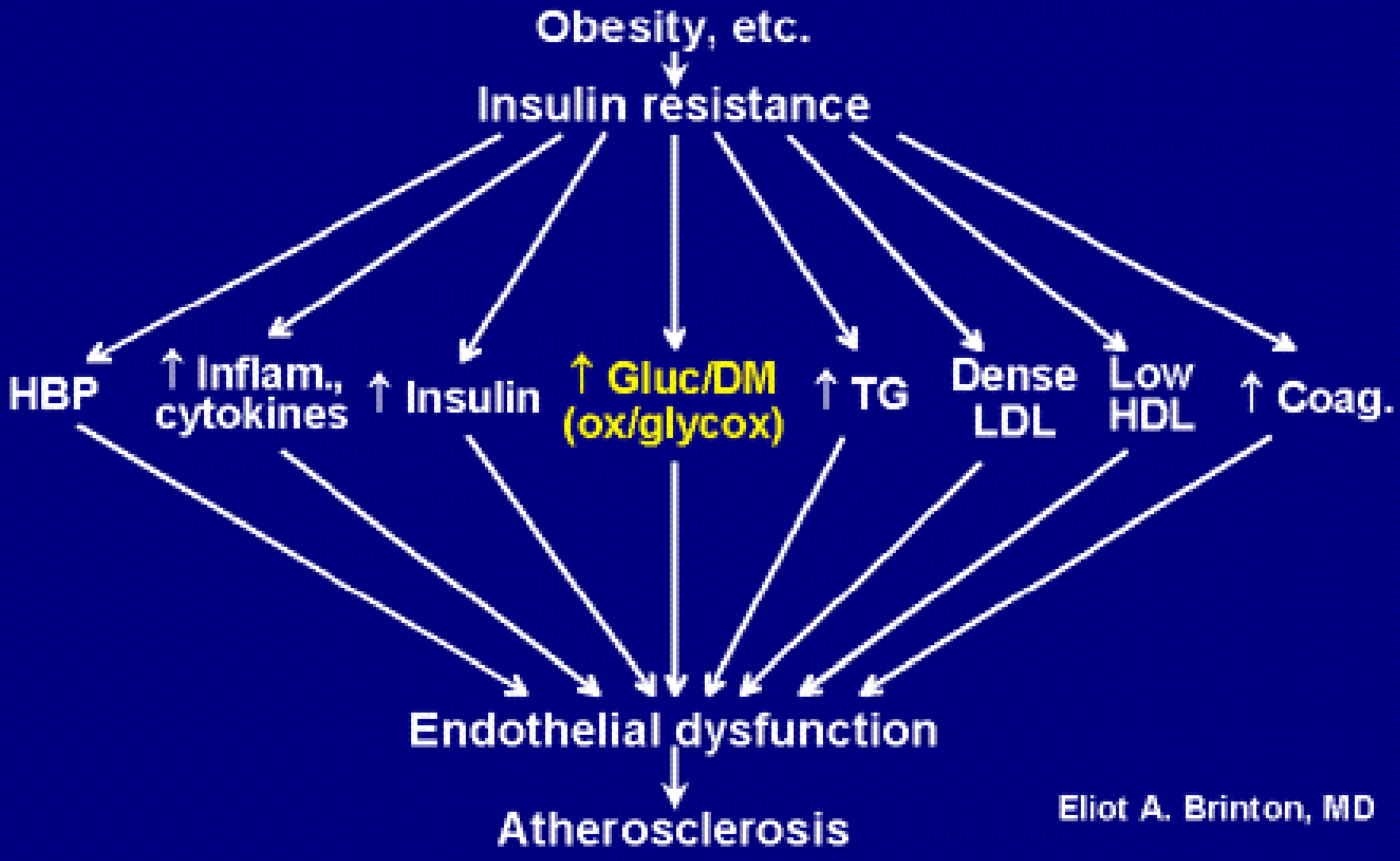
GLUCOTOXICITY

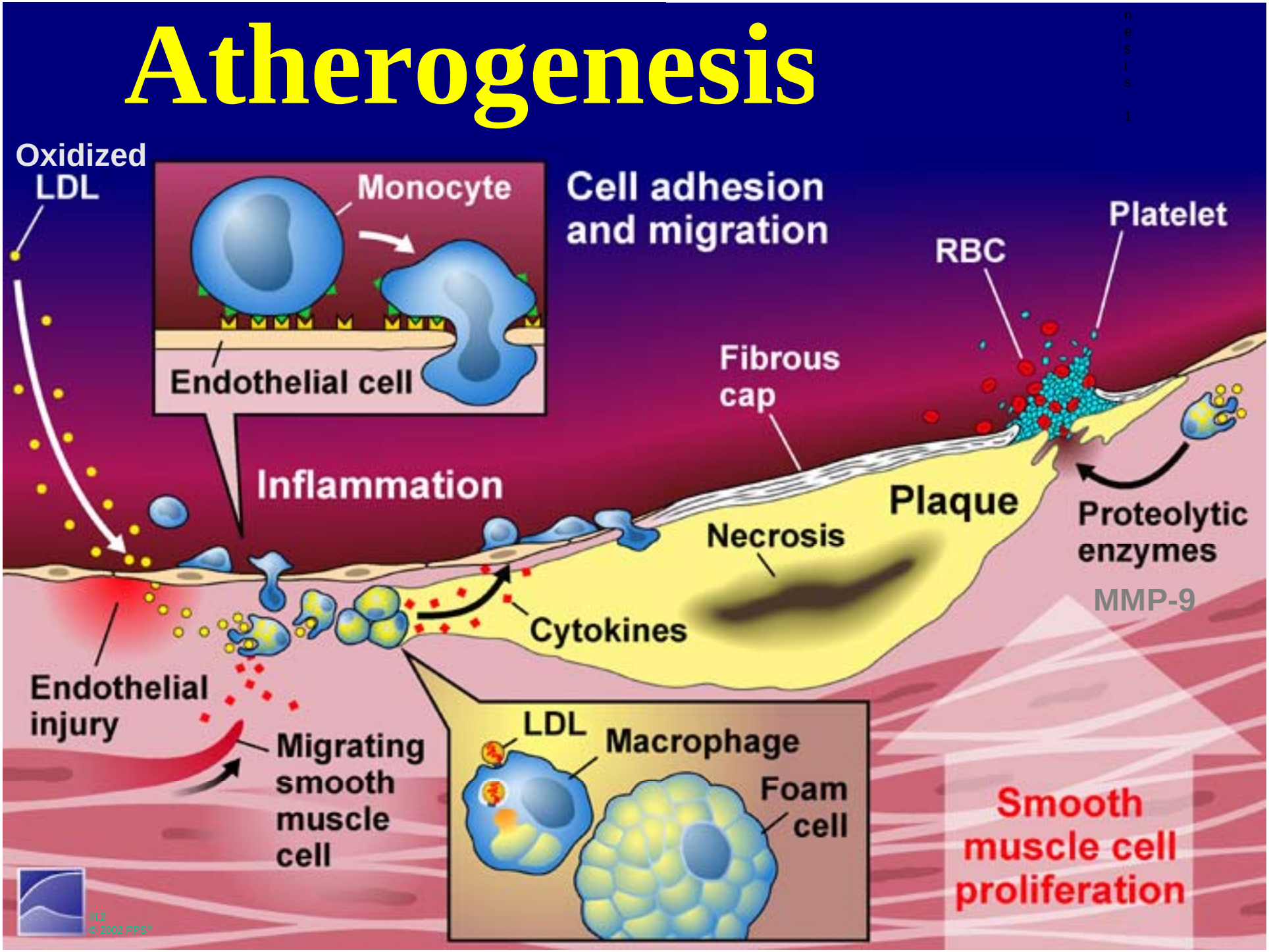
Dysfunctional Fat Cell

Excess production of:

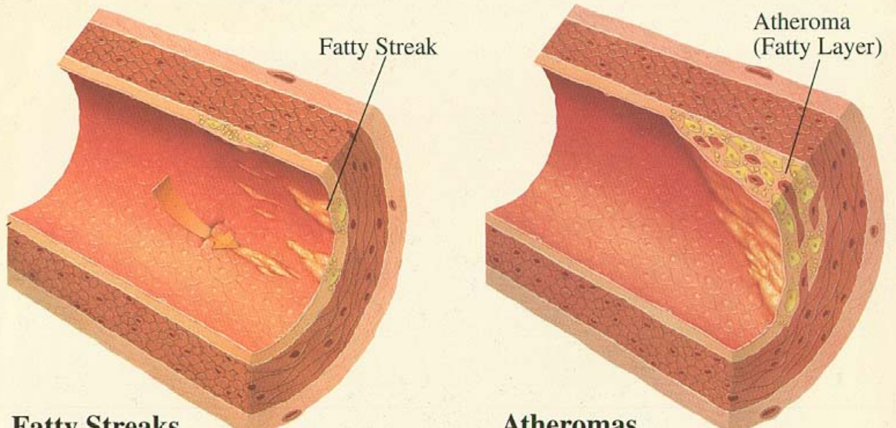
Free fatty acids
Interleukin-6
PAI (plasminogen activator inhibitor)
Leptin
Tumor necrosis factor
Resistin
Angiotensinogen

Interrelationship of Obesity, IR, Diabetes, and Atherosclerosis



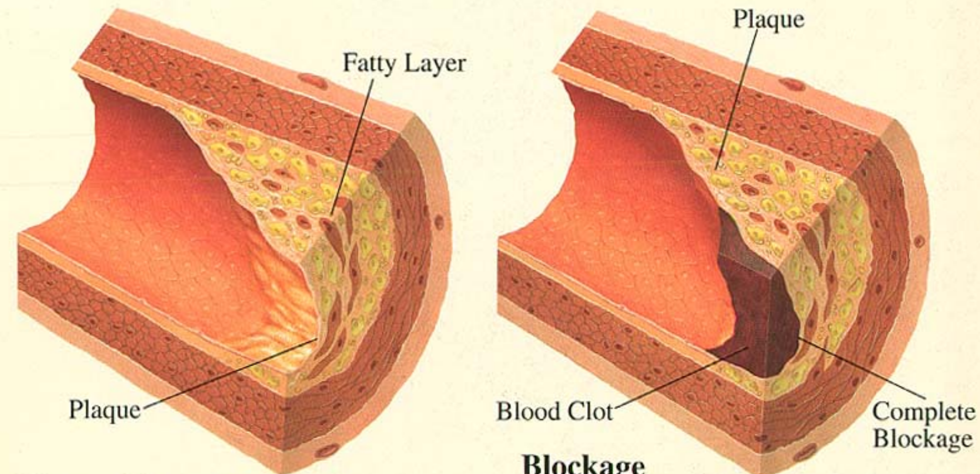

Atherogenesis
Oxidized LDL
Monocyte
Cell adhesion and migration
Platelet
RBC
Endothelial cell
Fibrous cap
Inflammation
Plaque
Necrosis
Proteolytic enzymes
MMP-9
Cytokines
Endothelial injury
LDL
Macrophage
Foam cell
Migrating smooth muscle cell
Smooth muscle cell proliferation
© 2002 PPS

Progression of Atherosclerosis



Fatty Streaks
Fatty materials in blood are deposited in the arterial wall, forming small ridges, which are called fatty streaks.

Atheromas
As more fatty substances from blood collect in arterial wall, fatty bulges called atheromas form.

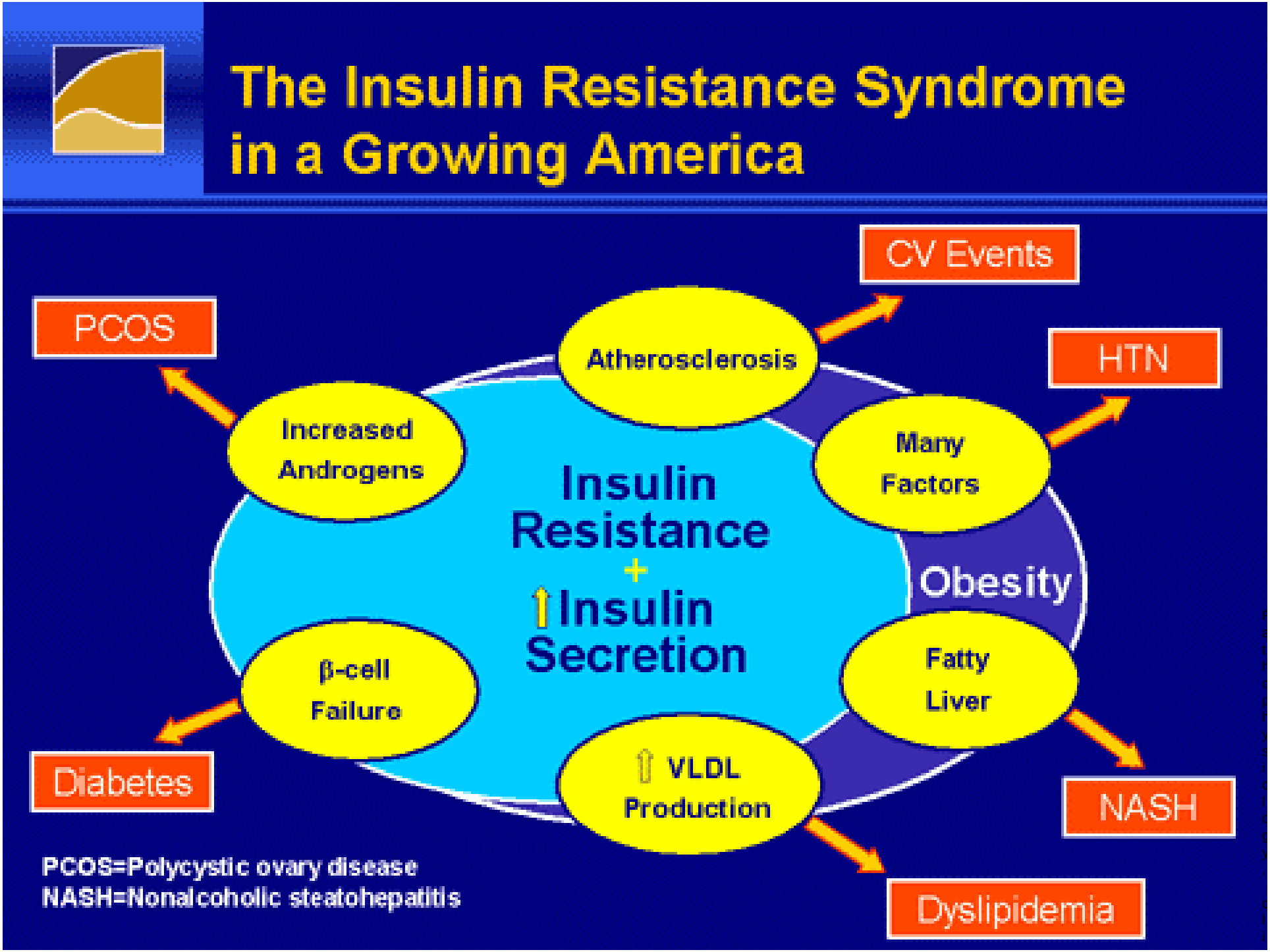


Fibrous Plaques
Scarlike tissue grows around atheromas, forming hardened plaques.

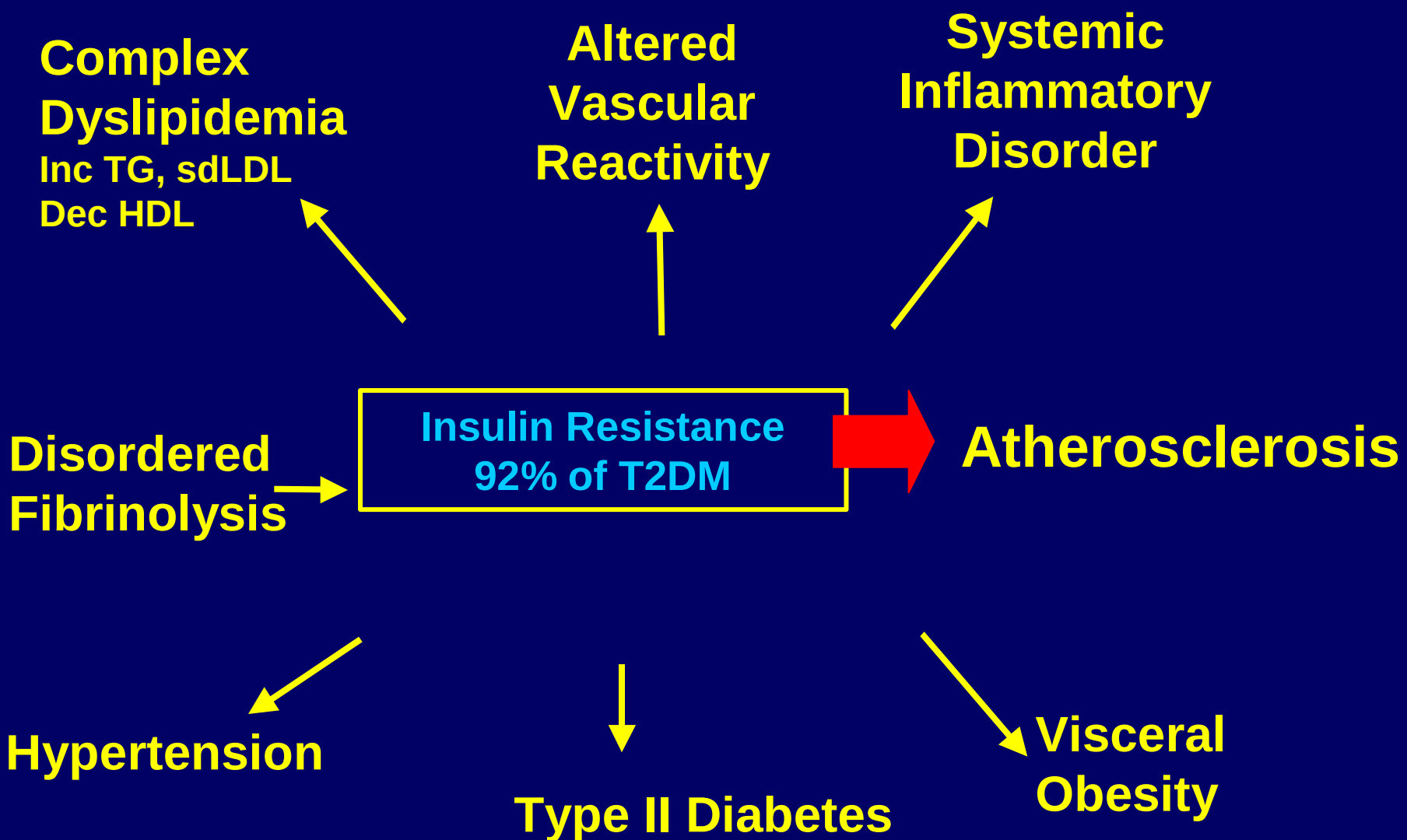
Blockage
Artery becomes clogged with plaque. Blood clots sometimes form in the narrowed artery, blocking blood flow.

enesis 2

The Insulin Resistance Syndrome in a Growing America



The Insulin Resistance Syndrome

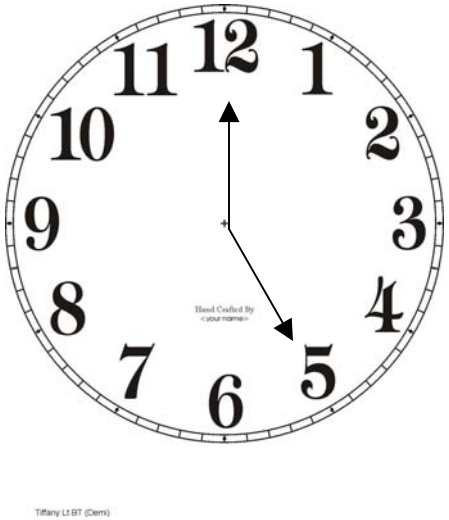


METABOLIC SYNDROME

CARDIOVASCULAR DISEASES

(macrovascular disease clock)

PREDIABETES



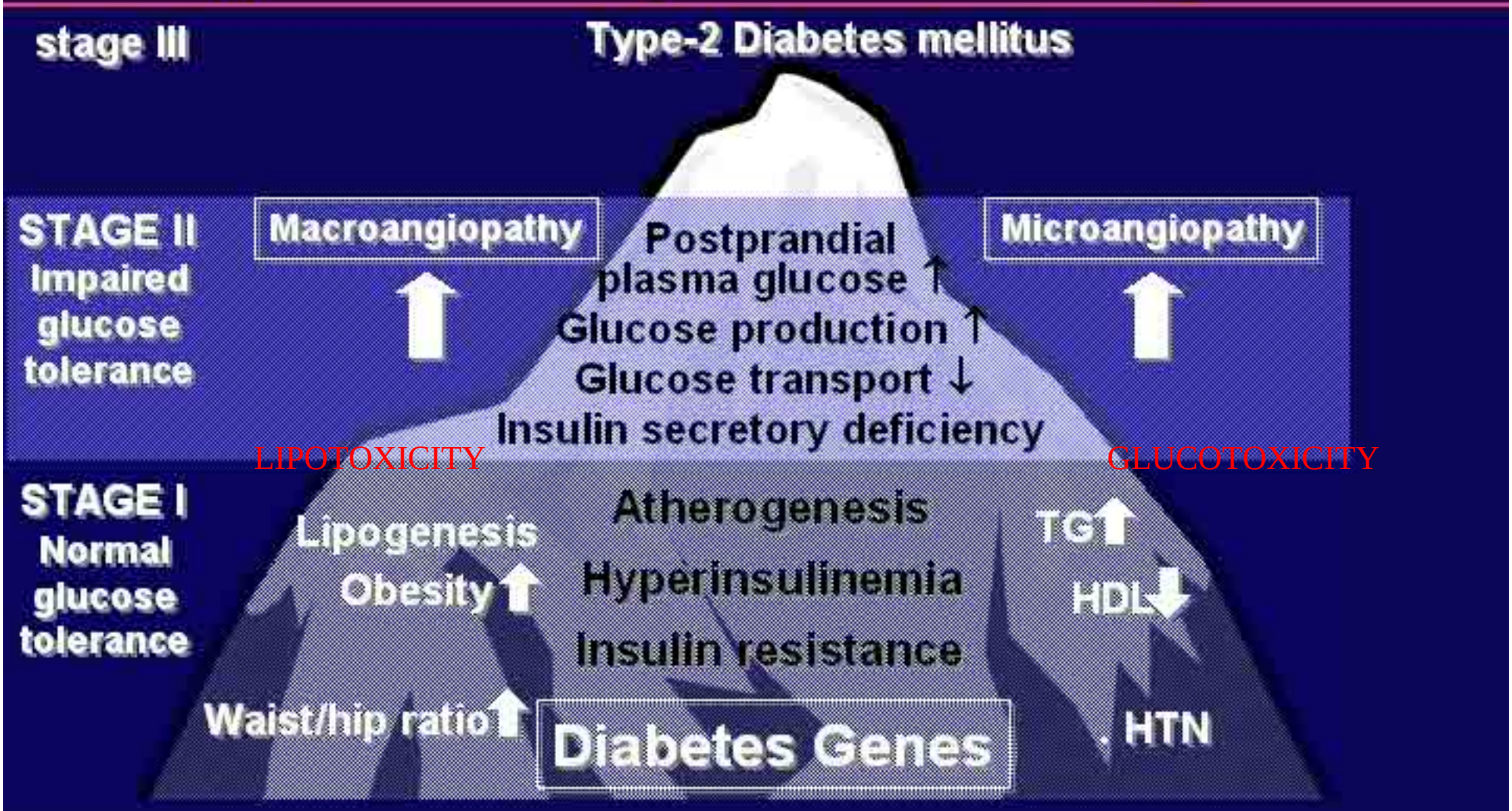
DIABETES COMPLICATIONS

(microvascular disease clock)

DIABETES

Pathophysiology

Type-2 DM: Tip of the Iceberg



Beck-Nielsen, J. Clin Invest 1994;21:1714

Atheroprevention in Diabetes vs Metabolic Syndrome (IR, IGT)

	DM-2	IR/Metabolic Syndrome
Prevalence (US)	~16M	~50M
Diagnosed	~50%-70%	~0.1%-5%?
Increase CHD	2-4 x	1.5-3 x
CHD Mechanism	Multiple	All but glycemia
Gender Effect	F>M (risk F=M)	F>M (risk F=M)
Basic Rx	Exer, wt loss, metformin, TZD	Exer, wt loss, TZD, metformin
Dyslipidemia	Low HDL, HTG, SDLDL	Low HDL, HTG, SDLDL
LDL-C Goal Adj.	-30 mg/dL	-20 mg/dL
Dyslip. Rx	Statin, Fibr, NA	Statin, Fibr, NA

Eliot A. Brinton, MD

The Insulin Resistance Syndrome

Clinical Manifestations

Central obesity
Glucose intolerance
Atherosclerosis
Hypertension
Polycystic ovary syndrome

Biochemical Abnormalities

Carbohydrate:

Insulin resistance
Hyperinsulinemia

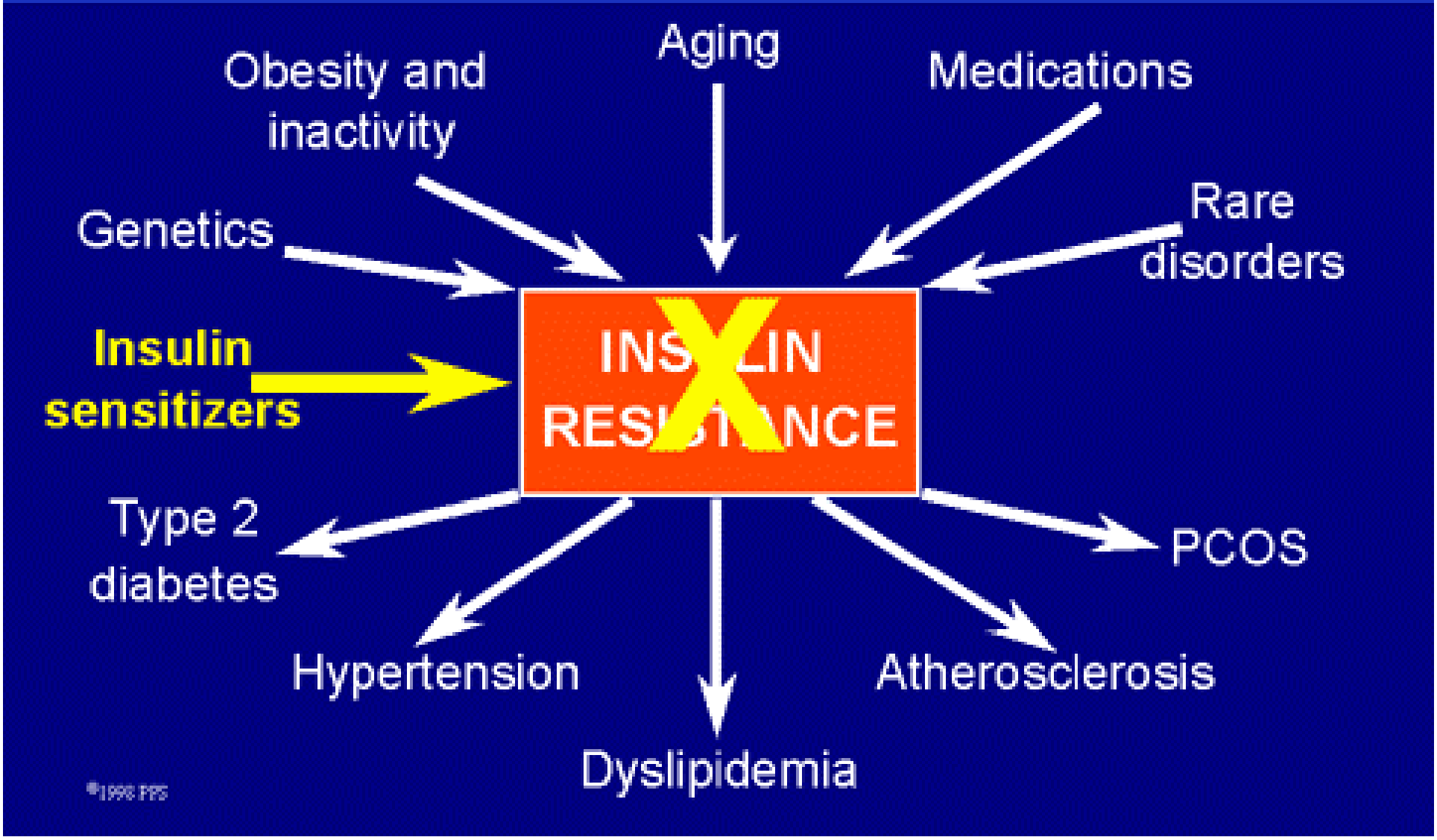
Lipid:

High TG
Low HDL-C
Small, dense LDL particles

Fibrinolysis:

Increased PAI-1

Insulin-Sensitizing Drugs: Opportunity for Disease Prevention



AHA/NHLBI/ADA: Clinical management of the metabolic syndrome

- Lifestyle modification of underlying risk factors
  - Weight loss
  - Increased physical activity
  - Modification of atherogenic diet
- Treat metabolic risk factors
  - Hypertension
  - Atherogenic dyslipidemia: LDL-C is No 1 priority
  - Prescribe aspirin if 10-year CHD risk is ≥10%
  - Insulin resistance

Grundy SM et al. *Circulation.* 2004;109:551-6.

NCEP/Framingham risk scores: Estimate of 10-yr CHD risk in men without CHD

Age (y)	20–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79
Points	–9	–4	0	3	6	8	10	11	12	13

Total-C (mg/dL)	Points: Age (y) 20–39	40–49	50–59	60–69	70–79
<160	0	0	0	0	0
160–199	4	3	2	1	0
200–239	7	5	3	1	0
240–279	9	6	4	2	1
?280	11	8	5	3	1

HDL-C (mg/dL)	Points
?60	–1
50–59	0
40–49	1
<40	2

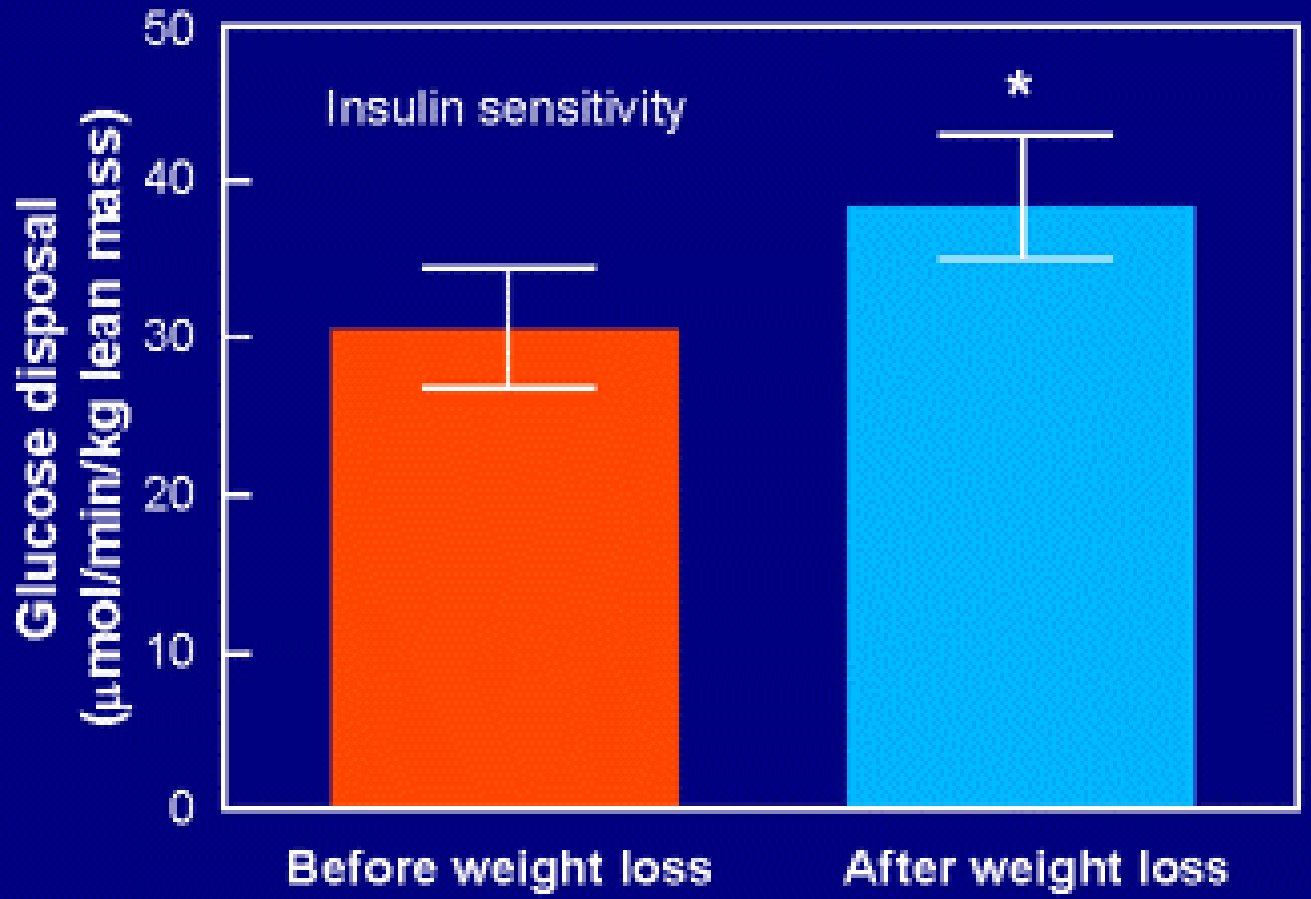
Age (y)	20–39	40–49	50–59	60–69	70–79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

Systolic BP (mm Hg)	Points: Untreated	Treated
<120	0	0
120–129	0	1
130–139	1	2
140–159	1	2
?160	2	3

Point total:	<0	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	>17
10-yr risk (%)	<1	1	1	1	1	1	2	2	3	4	5	6	8	10	12	16	20	25	?30

Reilly MP, Rader DJ. *Circulation*. 2003;108:1546-51.

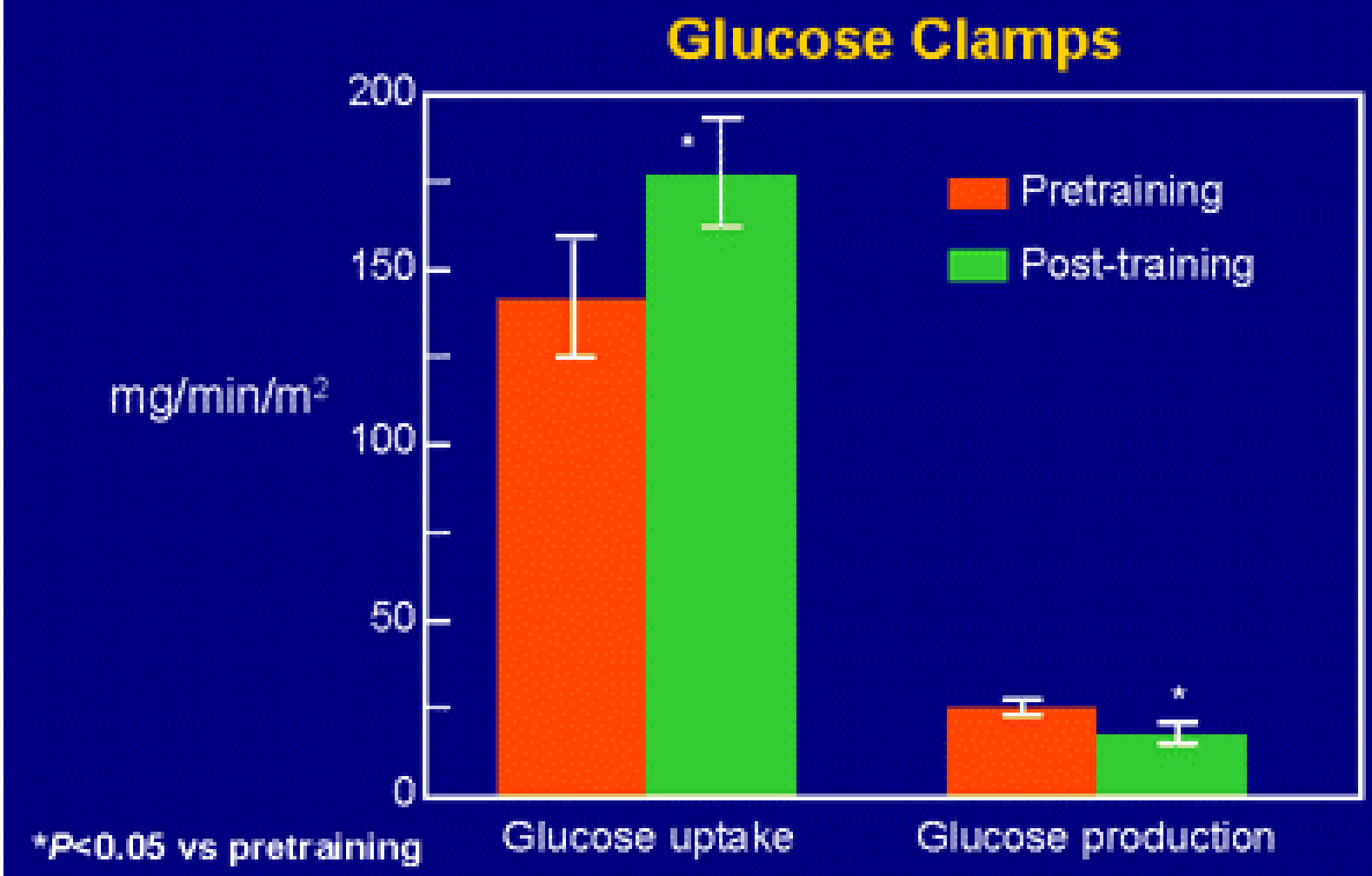
Short-term Weight Loss Improves Insulin Sensitivity



*$P<0.05$ before weight loss

Franssila-Kallunki A et al. *Am J Clin Nutr.* 1992;55:356-361.

Aerobic Exercise Improves Insulin Sensitivity



*P<0.05 vs pretraining

DeFronzo R et al. *Diabetes*. 1987;36:1379-1385.

Public and Professional Health Implications

- Programs to motivate activity
- Health professionals as role models
- An attack on childhood obesity

Obesity rates in preschool age children (2-5 years) and adolescents (12-19) have doubled in three decades

Obesity rates in children 6-11 has tripled in three decades